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Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

This issue is in honor of
Thomas M. McMillan, M.D
retiring Editor-in-Chief

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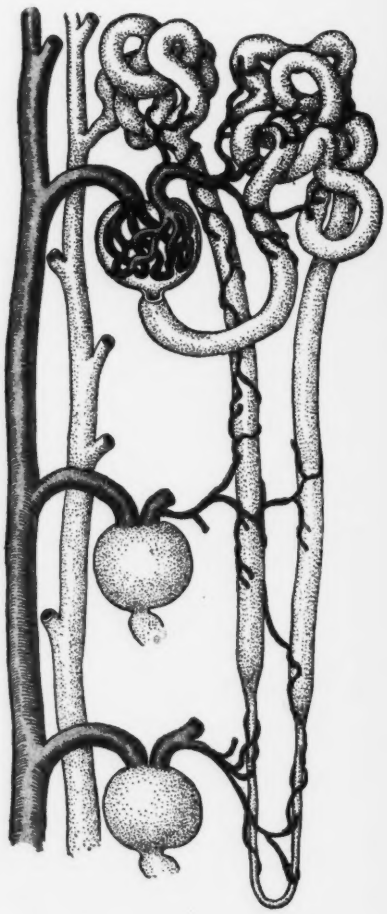

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Thomas McMillan, M.D

retiring Editor-in-Chief

Circulation, Volume XIII, January 1956

Thomas M. McMillan, M.D.

IT WAS with mixed feelings that I agreed to write this foreword for the special issue of CIRCULATION dedicated to Tom McMillan. The opportunity to speak publicly of a close friend was accepted with joy, tempered by the realization that the major purpose of this issue is to say at least a temporary farewell to the one person who has done more than any other to make this journal the foremost in its field. And farewells to those whom we love, however gay the celebration, can never be fundamentally other than sad.

It is probable that most of those who read these words have never known Tom as a person, but only as a thoughtful and distinguished editor. He first became famous in that capacity during the years 1946 to 1950, when he served as Editor in Chief of the AMERICAN HEART JOURNAL, then the official journal of the American Heart Association. When CIRCULATION was created as the official journal of the Association in 1950, his unusual abilities had been demonstrated so convincingly that no other person was considered for the position of its Editor-in-Chief.

Hundreds of perceptive authors and readers have realized that he gave unusual attention to manuscripts and proofs, but few could possibly realize how much time and thought he gave except those who have been with him day after day in his home or his summer camp. For five years this journal has been his one major interest, aside from his family. To it he has given most of his thought and energy, his days and evenings, week-ends and holidays, and a large share of every so-called vacation. This can be said without hesitation, for it has been my happy privilege to stand within the circle of his friendship for many years, to know the lovely spirit of his home, to watch him spending happy hours of golden afternoons poring over proofs when he should have been swimming or seeking the elusive bass that (according to rumor) live in Bixby Lake. Perfection may be the goal of every editor worthy of the name, but surely none has pursued that ideal more persistently than he, or with greater determination and hope. That he has been successful beyond the brightest dreams of those who founded CIRCULATION no one will doubt except Tom himself.

The first ten volumes of this journal will stand as a lasting monument to his ability and his consecration to the work that he loved. But he has created something else which, even though invisible and intangible, he may regard as much greater: the respect, admiration and abiding affection of all who have been privileged to know him. His students, associates and friends are agreed that few indeed have been blessed with such a rare combination of qualities: intelligence and understanding, complete sincerity, patience and tolerance, an unfailing gentleness rarely encountered in men, a sweet and happy disposition. The years in Philadelphia have taken away none of the consideration for others or the charming graciousness that he brought from his Alabama home. His inability to think or speak harshly of anyone has been an inspiration to those who recognize it as strength, not weakness, as another manifestation of a warm and lovable personality.

Though we say farewell to him as Editor-in-Chief of this journal that he has raised to such eminence, all who have worked with him will continue to cherish his friendship and seek his companionship. This is especially true of the members of the Editorial Board and of the Publications Committee, since they have been privileged to work more closely with him than most of his associates. But all those with whom he has shared the grace of his presence and the generous warmth of his personality will not easily allow these precious gifts to be withdrawn. Within the past few days he has given up the editorship of a famous journal, but he can never lose the affection and trust of those whom he has helped and influenced.

These inadequate words are written by one of the hundreds of friends whose hearts are united in gratitude for all that he has done and in the hope that his coming years will be rich in happy activities. Now that he has laid aside his editorial burdens, he may even find time to prove that there *are* bass in that lake!

H. M. Marvin, M.D.

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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

The Hemodynamic and Metabolic Interrelationships in the Activity of Epinephrine, Norepinephrine and the Thyroid Hormones

By WILLIAM R. BREWSTER, JR., M.D., JAMES P. ISAACS, M.D., PATRICIA F. OSGOOD, A.B. AND THELMA L. KING, R.N.

The hemodynamic and metabolic effects of a total sympathetic block and of the infusion of *l*-epinephrine or *l*-norepinephrine were studied in 27 euthyroid dogs and in 31 thyroid-fed dogs. The physiologic changes produced by increased concentrations of the thyroid hormones were abolished by preventing the reflex release of epinephrine and norepinephrine with a total sympathetic block. The inotropic, chronotropic and calorigenic effects of *l*-epinephrine and of *l*-norepinephrine were found to be increased by thyroid feeding. It is concluded that there is a dynamic interrelationship between the thyroid hormones and those of the adrenal medulla and sympathetic nerve endings. The hemodynamic and metabolic changes of thyrotoxicosis are not the result of the isolated activity of the thyroid hormones, but rather are due to the physiologic effects of epinephrine and norepinephrine, as augmented by the thyroid hormones. Studies indicate that *l*-norepinephrine is the predominant mediator of the changes produced by thyroid feeding.

PHYSIOLOGISTS have long recognized that the thyroid hormones are fundamentally important in the regulation of the quantitative metabolic and hemodynamic response to epinephrine or norepinephrine. Clinical and laboratory investigators have reported an increase in all parameters of activity of epinephrine, norepinephrine or their combination, as adrenalin, in thyrotoxic man and in thyroid-fed or thyroxin-injected man and laboratory mammals.[1-24] Conversely, the calorigenic, hemodynamic and metabolic effects of the known sympathoadrenal hormones have been shown to be diminished or absent in hypothyroid man and animals.[1, 2, 4, 5, 9, 11, 14, 17, 19, 21-28]

That there is a fundamental relationship between the activity of the thyroid hormones and those of the adrenal medulla and sympathetic nerve endings is further indicated by the clinical reports of the successful use of sympathetic block in both the prevention and treatment of thyrotoxic "crisis" or "storm." A total or near total sympathetic block, produced either by the subarachnoid injection of procaine,[29-33] or by the intravenous injection of hexamethonium,[34] has been reported to be effective both in preventing or abolishing the physiologic manifestations of thyrotoxic crisis. The injection of the "sympatholytic" drug, phenoxybenzamine hydrochloride (Dibenzyline)[35] has been reported to prevent an increase in the oxygen consumption, following the injection of thyroxine.

Barker,[36] in a thorough review of the mechanism of action of the thyroid hormones, drew attention to the need for a technic which would

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A preliminary report of this work appeared in abstract form in Federation Proc. **13:** 17, 1954.

Dr. Brewster is a Research Fellow of the American Heart Association.

quantitate the physiologic interrelationship between the thyroid and the sympathoadrenal hormones as follows: "Despite some conflicts, from the evidence thus far discussed emerges the currently prevalent concept that the normal thyroid gland functions to maintain the metabolic activity of most of the tissues of the body. Innervation, either somatic or visceral, is not essential to this effect, but *there has been no procedure devised to determine a possible nerve borne reinforcing action.*"

The need for a technic, to separate the physiologic effects of the thyroid hormones from those of epinephrine and norepinephrine in the intact animal, is met by the use of a total sympathetic block. In the experiments reported below, a total epidural preganglionic sympathetic block was used to abolish the reflex release of epinephrine and norepinephrine in dogs in which increased concentrations of the thyroid hormones had been produced by thyroid feeding. In this manner, the physiologic effects of the thyroid hormones were determined in the intact animal in the absence of epinephrine and norepinephrine. Furthermore, the effect of increased concentrations of the thyroid hormones upon the physiologic effects of either *l*-epinephrine or *l*-norepinephrine was determined by the individual infusion of these substances into euthyroid and thyroid-fed animals in which the reflex release of these hormones was prevented by a total sympathetic block.

When the actions of the thyroid and sympathoadrenal hormones are thus dissected, the results, presented below, indicate that the physiologic changes, resulting from thyroid feeding, are not the result of an effect of the thyroid hormones per se, but are the result, rather, of the interaction of the thyroid hormones with those of the adrenal medulla and sympathetic nerve endings, *l*-epinephrine and *l*-norepinephrine.

Method

(1) *Animals.* Mongrel male dogs varying in weight from 10 to 23.4 Kg. were used.

(2) *Feedings.* Dogs were fed with a high protein, high vitamin diet prior to and during the thyroid feeding. The diet consisted of horsemeat, 3 to 4 pounds per day; cow's milk, one-half quart per day; mashed dog food,* one-half pound per day; and multivitamin capsules, supplying daily 10,000 units of vitamin A, 4 mg. thiamin, 90 mg. ascorbic acid, 1000 units of vitamin D., 4 mg. riboflavine, 40 mg. nicotinamide, 2 mg. calcium pantothenate, 1 mg. pyridoxine hydrochloride.

(3) *Thyroid Feeding.* Animals were fed a daily amount of thyroid powder (U.S.P.)† calculated on the basis of 0.8 Gm. per kilogram of body weight.

Animals were studied after: (a) 7 to 10 days of thyroid feeding; (b) 11 to 15 days of thyroid feeding and (c) 17 to 22 days of thyroid feeding. Animals, included in the study, were limited to those which had consumed the maximum of their daily feeding. All dogs were studied 18 hours after their last feeding.

(4) *Anesthesia.* All dogs were anesthetized with thiopental sodium‡ for surgical preparation for the physiologic observations described below. Following surgical preparation and prior to the control studies, the dogs were allowed to recover from the thiopental anesthesia to the extent that all superficial reflexes were present and the animal would react to cutaneous or ocular stimuli with a motor response.

(5) *Body Temperature.* The rectal temperature of all animals was determined with a mercury thermometer. Immediately after the dogs were anesthetized, their oxygen consumption was determined without attempted control of the body temperature. Prior to the control determinations, but following the insertion of cardiac catheters and other preparations, the rectal temperature was lowered to 37.0 to 38.5 C. and was maintained within 1 C. of the control in most animals by the use of electric heating pads or of surface ice application. Although the effect of a total sympathetic block tended to result in a reduction in the body temperature and the infusion of either epinephrine or norepinephrine, to increase the body temperature, this was controlled by warming or cooling as indicated.

(6) *Technic of Total Epidural Sympathetic Block.* Following laminectomy at the level of L-2 or L-3, four polyvinyl catheters were introduced into the epidural space. The tips of the catheters were introduced to varying levels, approximating D-1, D-2, D-9 and S-1, to insure uniform distribution of the injected procaine solution throughout the epidural space. The total epidural preganglionic sympathetic block was produced by the injection of a 0.45 per cent procaine hydrochloride§ solution into the epidural space. Twenty-five to 35 ml. of the

* Purina Laboratory Chow, Ralston Purina Company, St. Louis.

† Armour and Company, Chicago, Illinois.

‡ Pentothal Sodium, Abbott Laboratories, Chicago, Ill.

§ Procaine HCl, Abbott Laboratories, Chicago, Ill.

procaine solution were injected at 25 to 30 minute intervals in order to maintain the block.

(7) *Criteria of the Completeness of a Total Epidural Sympathetic Block.* In the dog whose efferent preganglionic sympathetic fibers are incompletely blocked, the injection of procaine solution will result in a pressor and cardioaccelerator response of 2 to 4 minutes duration. The primary criterion of an effective total preganglionic sympathetic block was the complete absence of a pressor or cardioaccelerator response immediately following the injection of the procaine solution into the epidural space. Hemodynamic and metabolic studies were not done until the block had been established and maintained for at least an hour.

(8) *Oxygen Consumption and Ventilation of Dogs.* The dogs were either intubated with a no. 35 Magill endotracheal tube with an inflatable cuff or a similar tube was inserted and firmly tied in the trachea via tracheotomy. The determinations of the oxygen consumption in the control state and during the infusion of either *l*-epinephrine or *l*-norepinephrine were done with the animals ventilating spontaneously through a standard Benedict-Roth spirometer. During the maintenance of a total sympathetic block, it was found essential to ventilate the dogs mechanically in order to maintain normal alveolar and blood tensions of carbon dioxide and oxygen. The system described elsewhere was used[37] for the simultaneous intermittent positive pressure ventilation of the animal with an Emerson resuscitator* and spirometric determination of the oxygen consumption.

The values of oxygen consumption, reported below, are the average of a five-minute observation period after a steady pressure-volume state was reached.

(9) *Intracardiac and Extracardiac Pressures.* Pulmonary arterial pressure and left atrial pressures were obtained via no. 10 polyethylene catheters placed directly through small vessels approached by thoracotomy. Right atrial pressures were measured through a no. 10 catheter inserted into the right atrium via the external jugular vein. Femoral arterial pressures were obtained through a no. 19 Cournand needle inserted percutaneously or through a no. 10 polyethylene catheter ligated into the femoral artery.

Mean pressures were obtained by the use of saline, Tycos and Sanborn electromanometers.† All pressures were recorded on a four-channel Sanborn oscillograph. Full range and condenser-integrated mean pressures were obtained.

Following thoracotomy for the insertion of catheters, the chest was closed, and an intrathoracic cannula was left in place for the purpose of measuring the intrathoracic pressure.

(10) *Blood Volume.* The blood volume was maintained in all dogs throughout each experiment by replacing blood withdrawn for sampling with an equal volume of dextran.‡

(11) *Infusion of l-epinephrine or of l-norepinephrine.* When so indicated, *l*-epinephrine hydrochloride§ or *l*-norepinephrine bitartrate‖ was infused through a femoral venous cannula at a rate of 1 μg. of active base per kilogram of body weight per minute. In terms of the molecular weight of base, 1 μg. of *l*-norepinephrine is 8.2 per cent greater than 1 μg. of *l*-epinephrine.

(12) *Piperoxan hydrochloride* (Benzodioxane) # was given, when indicated, in a dosage of 1 mg. per kilogram by injection into the femoral venous cannula.

Collection of Samples

Blood for mixed venous oxygen was drawn from the pulmonary arterial catheter. Blood was withdrawn from the femoral artery for the following: arterial oxygen content, pH, total carbon dioxide, hemoglobin, blood sugar, serum lactate and pyruvate, serum sodium, potassium, chloride and serum protein-bound iodine determinations. For determination of the oxygen content of arterial and mixed venous blood, 6 ml. was drawn into a 10 ml. syringe containing approximately 0.1 to 0.2 ml. of a 10 per cent heparin solution together with a small bead of mercury for thorough mixing of the blood on shaking. The blood was iced immediately, and the oxygen determinations usually were done within two hours of withdrawal. Blood for pH and carbon dioxide determinations was collected in oiled syringes, transferred under oil and iced. The pH determination was done within 15 to 60 minutes and the total carbon dioxide determination within two hours. Methods used in biochemical studies of blood are the same as presented elsewhere.[37, 38] Serum protein-bound iodine was done by the method of Barker.[39]

Calculations

(a) The body surface area in square meters was obtained with Meeh's formula, using Rubner's constant for the dog as follows:

$$Surface\ Area/M.^2 = 1.12\ (weight/Kg.)^{.667}$$

* From the J. H. Emerson Company, Cambridge, Mass.

† Sanborn Company, Cambridge, Mass.

‡ Plavolex, Wyeth Laboratories, Inc., Philadelphia, Pa.

§ Suprarenin, Winthrop Stearns, Inc., New York, N. Y.

‖ Levophed bitartrate, Winthrop Stearns, Inc., New York, N. Y.

Benodaine, Merck and Company, Rahway, N. J.

(b) The oxygen consumption is expressed as *milliliters per minute* as corrected to standard temperature and pressure.

(c) *The oxygen consumption (ml./M.² body surface area)* $= \frac{\text{Oxygen consumption ml./min. (S.T.P.)}}{\text{Surface Area } M.^2}$

(d) *Cardiac index (liters/min./M² body surface area)* $= \frac{\text{Oxygen consumption ml./M.}^2 \text{ min.}}{\text{Arterio-venous oxygen diff. (vol. \%)}} \times \frac{1}{10}$

(e) *Index of total peripheral resistance (dynes/cm.$^{-5}$/sec.)* $= \frac{FAm(mm.Hg) - RAm(mm.Hg)}{\text{Cardiac index (ml./sec.)}} \times 1332$

(f) *Index of pulmonary resistance (dynes/cm.$^{-5}$/sec.)* $= \frac{PAm\ (mm.\ Hg) - LAm\ (mm.Hg)}{\text{Cardiac index (ml./sec.)}} \times 1332$

(g) *Left ventricular stroke work index (gram meters)*

$$= \frac{FAm(cm.\ H_2O) - LAm(cm.H_2O) \times \text{Stroke volume index (ml./beat/M.}^2 \text{ body surface area)}}{100}$$

(h) *Right ventricular stroke work index (gram meters)*

$$= \frac{PAm(cm.H_2O) - RAm(cm.H_2O) \times \text{stroke volume index (ml./beat/M.}^2 \text{ body surface area)}}{100}$$

(i) *Stroke volume index*

$$= \frac{\text{Cardiac index (ml./min./M.}^2 \text{ body surface area)}}{\text{Heart rate (min.)}}$$

(j) Arterial carbon dioxide tensions were derived from the arterial serum pH and total carbon dioxide tensions using the nomogram of Singer and Hastings.[40]

Procedure

Studies described above were done on 27 euthyroid dogs and on 31 thyroid-fed dogs. The duration of thyroid feeding was as follows: (a) 10 dogs were fed thyroid for 7 to 10 days; (b) 10 dogs were fed thyroid for 11 to 15 days; and (c) 11 dogs received thyroid for 18 to 22 days. All dogs, both euthyroid and thyroid-fed, were studied as follows: (1) under light thiopental sodium anesthesia prior to surgical stimulation, (2) after surgical preparation and prior to a total sympathetic block, (3) during a 1 to 4 hour period following the establishment of a total epidural preganglionic sympathetic block and (4) with the total sympathetic block maintained to prevent the reflex release of epinephrine or norepinephrine by the animal, studies were done during the infusion of either *l*-epinephrine or of *l*-norepinephrine individually in different animals. During the above infusions, results, presented below, are from observations made 5, 30 and 60 minutes, following the start of the individual infusion; with the infusion continued, 1 mg. per kilogram of benzodioxane was injected. Its effects were studied 2 to 5 minutes following injection.

Results

Serum Protein Bound Iodine Concentrations. The serum protein-bound iodine concentration of the 27 euthyroid dogs averaged 1.7 μg. per 100 ml. Following thyroid feeding, the average serum protein-bound iodine concentrations were as follows: 7 to 10 days, 16.6 μg. per 100 ml.; 11 to 15 days, 18.1 μg. per 100 ml. and 18 to 22 days, 16.9 μg. per 100 ml. There was no significant difference in the serum protein-bound iodine concentrations, whether the dogs were fed thyroid for approximately 1 or 3 weeks.

Hemodynamic Results

Heart Rate

Effect of Thyroid Feeding. There is a progressive rise in the heart rates following thyroid feeding (fig. 1). Surgical stimulation (tables 1 and 2)* caused a further small increase in the heart rates of all groups of dogs. The relatively fast heart rates, seen in the control state (fig. 1) in all groups of dogs, are due to three factors: surgical stimulation, the extremely light level of thiopental anesthesia in the animals during the control studies and the well-documented vagal inhibitory effect of even light thiopental anesthesia.

Effects of a Total Sympathetic Block. When the reflex release of epinephrine and norepinephrine was abolished by a total sympathetic block, the heart rates of the thyroid-fed animals declined to levels that were identical to those of the euthyroid dogs with a total sympathetic block (fig. 1).

Effects of l-Epinephrine and of l-Norepinephrine Infusion. The infusion of either *l*-epinephrine or of *l*-norepinephrine into the thyroid-fed dogs resulted in increases in the average heart rates that were significantly greater than those observed in similarly infused

* At the request of the editor, tables 1 and 2 are being omitted. These will be furnished on request.

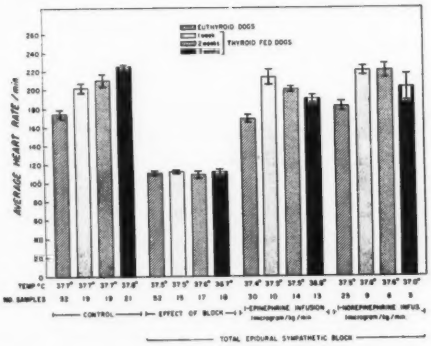

FIG. 1. Effect of thyroid feeding, total sympathetic block and the infusion of *l*-epinephrine or *l*-norepinephrine on the heart rate per minute in euthyroid and thyroid-fed dogs. All figures include the mean and the standard error of the mean.

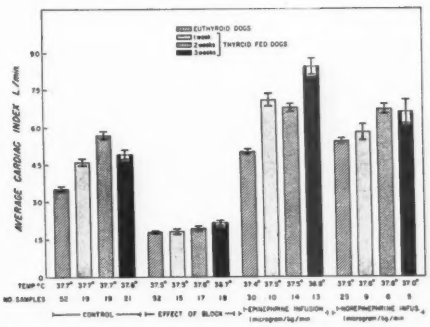

FIG. 2. Effects of thyroid feeding, total sympathetic block and the infusion of either *l*-epinephrine or *l*-norepinephrine on the average cardiac indices of euthyroid and thyroid-fed dogs.

euthyroid dogs (fig. 1). However, inasmuch as the mean femoral arterial pressures during the infusion of *l*-epinephrine and of *l*-norepinephrine were lower in the thyroid fed dogs than in the euthyroid dogs, it became essential to compare the average heart rates of the dogs at comparable arterial pressure levels to rule out reflex baroreceptor inhibition as an important factor influencing the heart rates. For this purpose Benzodioxane was used. It has been shown[41] that Benzodioxane, in doses of 1 mg. per kilogram, intravenously, inhibits the systemic vasoconstrictor effects, but does not inhibit the chronotropic effects of epinephrine. When the mean femoral arterial pressures of both the euthyroid and thyroid fed dogs were reduced to the same levels, following the injection of Benzodioxane (fig. 3) during the infusion of epinephrine, the average heart rate of the thyroid-fed dogs remained greater than that of the euthyroid dogs. The same principle held true in the case of *l*-norepinephrine infusion (fig. 4). Thus, it can be concluded that the feeding of thyroid results in an increase in the positive chronotropic effects of both *l*-epinephrine and *l*-norepinephrine.

Cardiac Index

Thyroid Feeding. Thyroid feeding produced significant increases in the cardiac indices of all groups of thyroid fed animals (fig. 2, tables 1 and 2).* The greatest average increase occurred in the dogs fed thyroid for 11 to 15 days.

Total Sympathetic Block. Following a total sympathetic block, the average cardiac indices of the thyroid-fed dogs decreased to values that were not significantly different from those observed in the euthyroid dogs with a total sympathetic block (fig. 2).

Infusion of l-Epinephrine and l-Norepinephrine. During the infusion of either *l*-epinephrine or of *l*-norepinephrine in all groups of thyroid-fed dogs (fig. 2), there was a greater rise in the average cardiac indices than was observed in similarly infused euthyroid dogs. In order to determine whether the positive inotropic effects of epinephrine and norepinephrine were increased by thyroid hormones, it was necessary to quantitate, as well as possible, all factors that may vary the total blood flow per minute. In the presence of a constant blood volume, freely available for ventricular filling, the important determinants of minute blood flow are: (1) the contractile force of the ventricles, (2) the heart rate and (3) the resistance which the peripheral or pulmonary vascular bed offers to the effective emptying of blood from the left and right ventricles respectively. The following relationship, then, exists in determining the cardiac index:

$$\textit{Cardiac Index} \propto \frac{(\textit{Force of Ventricular Contraction})(\textit{Rate})}{\textit{Pulmonary or Peripheral Resistance}}.$$

* See footnote p. 4.

To shed further light on the individual factors responsible for the greater cardiac indices of the thyroid-fed dogs during epinephrine or norepinephrine infusion, 1 mg. per kilogram of benzodioxane was injected intravenously in both euthyroid and thyroid-fed dogs during the infusion of either epinephrine or norepinephrine. In this dosage, sympatholytic drugs, similar to benzodioxane, have been shown to reduce or abolish the peripheral vasoconstrictor component of activity of *l*-norepinephrine, and in the case of *l*-epinephrine both to abolish the peripheral vasoconstrictor component of activity and to result in an active vasodilation.[42] Benzodioxane does not alter the quantitative inotropic or chronotropic effects of either *l*-epinephrine or *l*-norepinephrine.[43]

As shown in figure 3, the injection of 1 mg. per kilogram of benzodioxane, during epinephrine infusion in the euthyroid dogs, resulted in a fall in the average mean arterial pressure from 169 mm. Hg to 64 mm. Hg, this fall being the result of an intense peripheral vasodilation. Consequent to this drop in peripheral resistance, there was an increase in the cardiac index of the euthyroid dogs from 4.21 to 6.23 liters per minute. The injection of 1 mg. per kilogram of benzodioxane into the thyroid-fed dogs during the infusion of epinephrine,

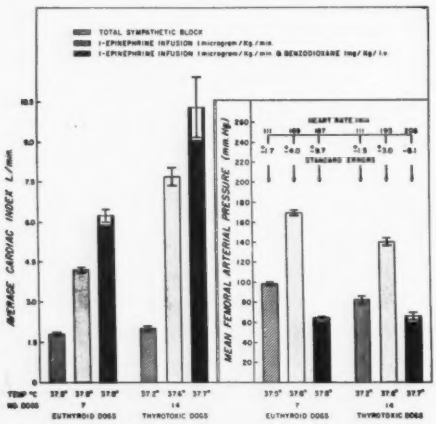

FIG. 3. Effects of the injection of Benzodioxane 1 mg. per Kg. intravenously on the cardiac indices, mean femoral arterial pressures and heart rates of euthyroid and thyroid-fed dogs, during the infusion of *l*-epinephrine at a rate of 1 μg. per Kg. per minute intravenously.

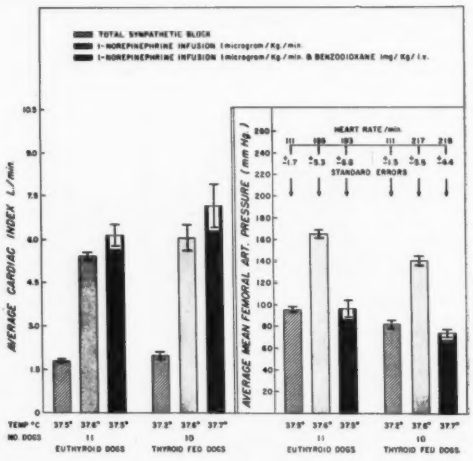

FIG. 4. Effects of the injection of Benzodioxane 1 mg. per Kg. intravenously on the cardiac indices, mean femoral arterial pressures and heart rates of euthyroid and thyroid-fed dogs during the intravenous infusion of *l*-norepinephrine at a rate of 1 μg. per Kg. per minute.

while the mean femoral arterial pressure fell to the same levels observed in euthyroid dogs, resulted in an increase in the average cardiac index from 7.80 to 10.23 liters per minute. This illustrates that with the inotropic effect of epinephrine remaining constant, and, therefore, with the effective ventricular contractile force remaining constant, the cardiac index (the total minute volume of blood flow) increases as a result of a decrease in resistance to effective left ventricular emptying.

Much more important, this experiment may be used to demonstrate that thyroid feeding caused an increase in the positive inotropic effect of *l*-epinephrine. Evidence for this is the fact that the average cardiac index of the thyroid-fed dogs during epinephrine infusion alone (7.80 liters per square meter per minute) is greater than that of the euthyroid dogs in which the peripheral resistance has been lowered by the injection of Benzodioxane during the infusion of *l*-epinephrine (6.23 liters per square meter per minute).

The increases in the average cardiac indices, observed to occur in both euthyroid and thyroid-fed dogs following the injection of Benzodioxane during the infusion of epinephrine, were

greater than can be accounted for by an increase in the heart rates alone. The increase in cardiac index was proportional to the increase in stroke volume output (tables 1 and 2).* Figure 4 shows that similar, though not as great, increases in the average cardiac indices occurred following the injection of benzodioxane during the infusion of *l*-norepinephrine.

In summary, the infusion of either *l*-epinephrine or of *l*-norepinephrine into thyroid-fed dogs resulted in increases of the average cardiac indices that were significantly greater than those observed in the euthyroid animals. Three factors have been shown to play an important role in the increased cardiac indices of the thyroid-fed animals during the infusion of the catechol amines, as contrasted to similarly treated euthyroid animals: (1) an increase in the inotropic effects of epinephrine and norepinephrine by the increased concentrations of the thyroid hormones, (2) an increased heart rate, due to an increase in the chronotropic effects of epinephrine and norepinephrine by the thyroid hormones and (3) a decrease in the resistance to left ventricular emptying in the thyroid-fed animals, as contrasted to the euthyroid animals during the infusion of either epinephrine or of norepinephrine.

Right and Left Ventricular Stroke Work Indices and the Mean Right and Left Atrial Pressures

To examine the effects of drugs, hormones or pathologic events upon the energetics of the ventricles, it is necessary to examine these indirectly by measuring the capacity of the ventricles for doing work. To study the effective work of the ventricles, it has been emphasized that it is necessary to quantitate the mechanical work done by the individual ventricle in relationship to its filling pressure. Starling's law of the heart has been recently clarified and confirmed to apply in the dog[44-48] and in man.[49] It has been demonstrated that both *l*-epinephrine and *l*-norepinephrine, by virtue of their positive inotropic effects, are capable of increasing the energy of ventricular contraction per unit of ventricular filling pressure.[44, 46]

Results demonstrated in figures 5 to 8 were

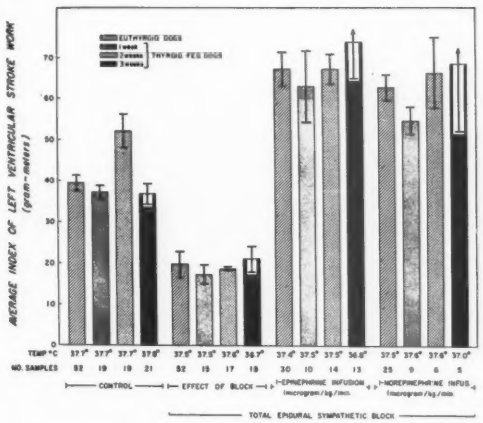

FIG. 5. Effects of thyroid feeding, total sympathetic block and the infusion of *l*-epinephrine or *l*-norepinephrine on the average indices of left ventricular stroke work in the euthyroid and thyroid-fed dogs.

obtained in investigating the direct effects of the thyroid hormones per se on the energetics of the ventricles, as contrasted to the effects of the thyroid hormones in augmenting the inotropic effects of epinephrine and norepinephrine.

Effects of Thyroid Feeding. There was a significant increase in the left ventricular stroke work relative to the average left atrial mean pressure in the thyroid-fed dogs (figs. 5 and 6).

There was a progressive rise in the right ventricular stroke work of the thyroid-fed

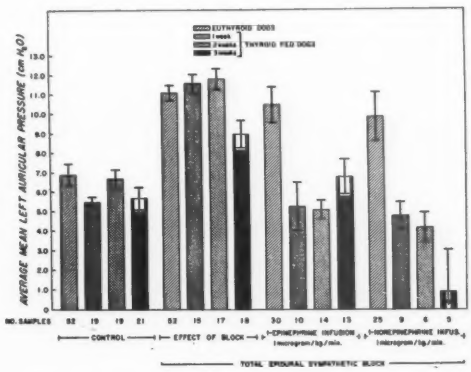

FIG. 6. Effects of thyroid feeding, total sympathetic block, and the infusion of *l*-epinephrine or *l*-norepinephrine on the average left atrial mean pressure in euthyroid and thyroid-fed dogs.

* See footnote p. 4.

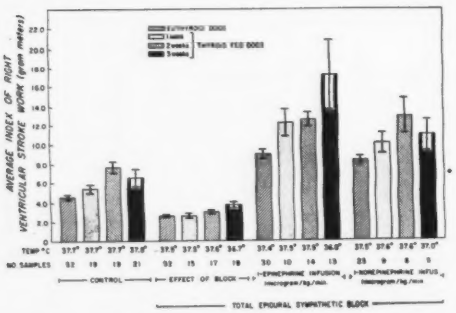

FIG. 7. Effects of thyroid feeding, total sympathetic block and the infusion of *l*-epinephrine or *l*-norepinephrine on the average indices of right ventricular stroke work in euthyroid and thyroid-fed dogs.

animals, compared with that of the euthyroid animals. Relative to the right atrial mean pressure, this rise was not significant in the dogs fed thyroid for one week, but was highly significant in the dogs fed thyroid for a two to three-week period (figs. 7 and 8).

Effects of a Total Sympathetic Block. Figures 5 and 6 demonstrate that, following a total sympathetic block, the left ventricular stroke work of the euthyroid and thyroid-fed dogs decreases to levels that are not significantly different. During the maintenance of a total sympathetic block, the average left atrial mean pressures of all groups of animals rose above the levels observed in the control state. There was no significant difference in the average left atrial mean pressures observed in the euthyroid

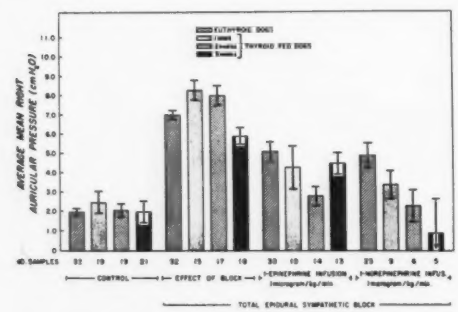

FIG. 8. Effects of thyroid feeding, total sympathetic block and the infusion of *l*-epinephrine or *l*-norepinephrine on the average right atrial mean pressures of euthyroid and thyroid-fed dogs.

dogs and the thyroid-fed dogs with a total sympathetic block.

Figure 7 and 8 demonstrate that there was no significant difference in the average right ventricular stroke works and average right atrial mean pressures of euthyroid dogs and one- and two-week thyroid-fed dogs during a total sympathetic block. Although within the range of values observed in euthyroid-blocked dogs, the average right ventricular stroke work of the 3-week thyroid-fed animals was a little higher than that of the euthyroid dogs per unit of right atrial mean pressure.

When the right and left ventricular stroke work and right and left atrial mean pressures of all thyroid-fed dogs are compared with those of all euthyroid dogs during the maintenance of a total sympathetic block (tables 1 and 2)*, no significant difference existed between these two groups of animals.

During total sympathetic block, the close correlation between the mean right and left ventricular stroke work and the average right and left atrial mean pressure of the euthyroid and thyroid-fed dogs, despite marked differences in the circulating thyroid hormone concentrations in the two groups, indicates that the thyroid hormones, in the absence of circulating epinephrine and norepinephrine, have no direct effect upon the function of the ventricles.

Effects of l-Epinephrine or of l-Norepinephrine Infusion. During the infusion of either *l*-epinephrine or of *l*-norepinephrine at rates of 1 μg. per kilogram per minute, there were equivalent increases in the average left ventricular stroke work of euthyroid and thyroid-fed dogs (fig. 5). In the thyroid-fed dogs, however, there was a greater reduction than in the euthyroid dogs in the average left atrial mean pressure, during epinephrine and norepinephrine infusion (fig. 6). The increase in the left ventricular stroke work of the thyroid-fed dogs per unit of left atrial mean pressure was significantly greater than that observed in the euthyroid group of animals.

The right ventricular stroke work of the thyroid-fed dogs, during the infusion of either epinephrine or norepinephrine, increased more

* See footnote p. 4.

than did that of the euthyroid dogs (fig. 7). Simultaneously, there was a greater decrease in the average right atrial mean pressure in the thyroid-fed animals during the infusions than was observed in the euthyroid animals (fig. 8). Thus, the effective right ventricular stroke work per unit of filling pressure, during the infusion of epinephrine or norepinephrine, was significantly greater in the thyroid-fed dogs than in the euthyroid dogs.

Effect of Benzodioxane Injection. Following the injection of Benzodioxane (1 mg. per kilogram, intravenously) during the infusion of either *l*-epinephrine or of *l*-norepinephrine in euthyroid and in thyroid-fed animals, there was a decrease in both the average left ventricular stroke works and in the average left atrial mean pressures (figs. 9 and 10). In general, there was an increase in the right ventricular stroke works, together with a fall in the average right atrial mean pressures. It is seen that both the right and left ventricular stroke works in the thyroid-fed dogs remain consistently higher per unit of filling pressure, following benzodioxane injection, than in the euthyroid animals. This is in keeping with the analysis of changes in the cardiac indices, presented above. The consistently higher ventricular stroke works of the thyroid-fed animals as compared with that of

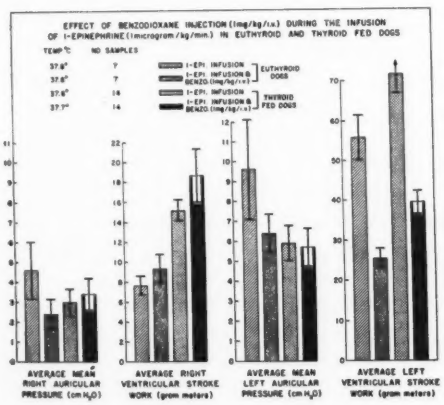

FIG. 9. Effects of Benzodioxane injection 1 mg. per Kg. intravenously during the infusion of *l*-epinephrine (1 μg. per Kg. per minute) in euthyroid and thyroid-fed dogs. Average right and left atrial mean pressures and average right and left ventricular stroke works.

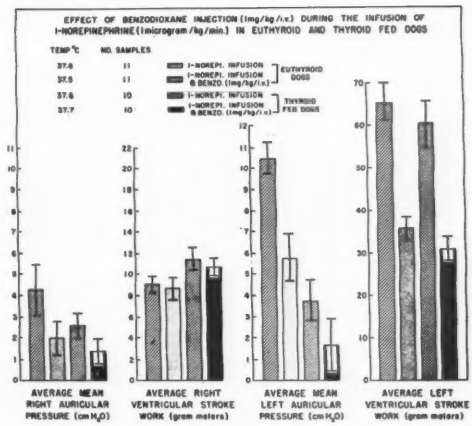

FIG. 10. Effects of Benzodioxane injection 1 mg. per Kg. intravenously during the infusion of *l*-norepinephrine (1 μg. per Kg. per minute) in euthyroid and thyroid-fed dogs. Average right and left atrial mean pressures and average right and left ventricular stroke work are shown.

the euthyroid dogs, following Benzodioxane injection during the infusion of either *l*-epinephrine and *l*-norepinephrine, is a further indication that an increase in the thyroid hormone concentrations will increase the positive inotropic effects of both *l*-epinephrine and *l*-norepinephrine.

Average Mean Femoral Arterial Pressures

There was no significant difference in the mean femoral arterial pressures of the euthyroid and thyroid-fed dogs in the control state (tables 1 and 2).*

Following a total epidural sympathetic block, the mean femoral arterial pressures of both the euthyroid and thyroid-fed dogs decreased. The pressures of the thyroid-fed animals, during the period of a sympathetic block, were 10 to 15 mm. Hg lower than these of the euthyroid dogs. Despite this difference, the average mean femoral arterial pressures of the thyroid-fed dogs fell well within the range of values observed in individual euthyroid animals with a total sympathetic block (tables 1 and 2).*

During the infusion of *l*-epinephrine or of *l*-norepinephrine, the average mean femoral

* See footnote p. 4.

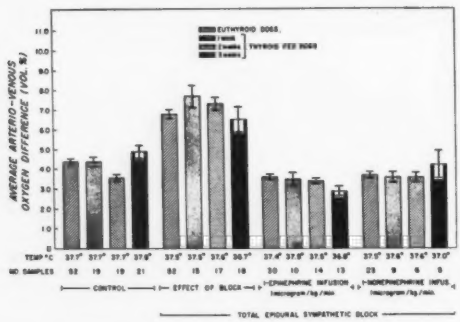

FIG. 11. Effect of thyroid feeding, total sympathetic block and the infusion of *l*-epinephrine or *l*-norepinephrine on the arteriovenous oxygen difference.

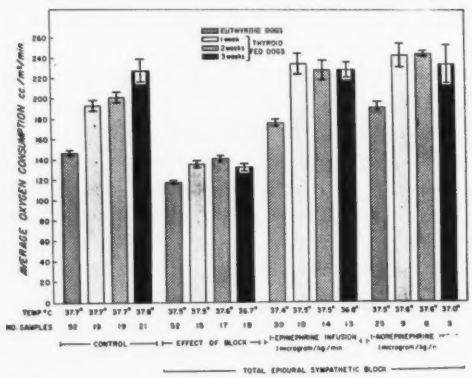

FIG. 12. Effect of thyroid feeding, total sympathetic block, and the infusion of *l*-epinephrine or *l*-norepinephrine on the oxygen consumption in cubic centimeters per square meter per minute in euthyroid and thyroid-fed dogs.

arterial pressures, as well as the calculated total peripheral resistance (tables 1 and 2)* of the thyroid-fed animals, were significantly lower than in the euthryoid dogs. Because of the changes in other variables, namely the heart rate, cardiac index and total peripheral resistance, the extent of rise of the average mean femoral arterial pressures alone did not serve an an index of potentiation of the physiologic activity of epinephrine and norepinephrine by the thyroid hormones.

Arteriovenous Oxygen Difference

There was no significant difference in the arteriovenous oxygen difference of the euthyroid and thyroid-fed dogs in the control state, following a total sympathetic block, or during the infusion of either *l*-epinephrine or of *l*-norepinephrine (fig. 11).

Metabolic Results

Oxygen Consumption

Effect of Thyroid Feeding. The average oxygen consumption of the animals under light thiopental sodium anesthesia prior to thyroid feeding was 130.9 ml. per M.² per minute (table 2).* Under identical circumstances, following thyroid feeding and prior to surgical preparation of the animals, increases in the average oxygen consumption of 50 ml., 54 ml. and 58 ml. per square meter per minute had occurred in the dogs fed thyroid for 1, 2 and 3 weeks, respectively. The difference in the average oxygen consumption of the thyroid-fed dogs, before and after surgical stimulation, was not statistically significant at the $p < .05$ level.

Effect of Total Sympathetic Block. Following a total sympathetic block, the average oxygen consumption (ml. per square meter per minute) of the thyroid-fed animals decreased to levels that were within the range of values observed in individual euthyroid dogs with a total sympathetic block (fig. 12). However, the average oxygen consumption of the thyroid-fed dogs remained higher statistically (at the $p < .05$ level) than the average of the euthyroid dogs with a total sympathetic block.

In view of this significantly higher oxygen consumption in the thyroid-fed animals during a total sympathetic block, figure 13 was prepared to show variations in the average oxygen consumption of the dogs in ml. per minute as well as in ml. per square meter per minute. During thyroid feeding, the dogs lost an average of 1.7 Kg. body weight. In contrast to the euthyroid group of animals, in which subcutaneous fat constituted an appreciable proportion of their body weight, the thyroid-fed group of dogs showed little or no subcutaneous fat. The surface area (M.²) of the dog was calculated from the dog's weight directly, using Meeh's formula with Rubner's constant. Since fat has a relatively low oxygen consumption, as

* See footnote p. 4.

contrasted to lean body mass, a discrepancy can be expected in the comparison of the oxygen consumption on a body weight basis in dogs where the amount of fat per total weight is different. Figure 13 shows that, prior to thyroid feeding, the average oxygen consumption in ml. per square meter per minute of the dogs was 130.9, while the average oxygen consumption in ml. per minute was 93.3. During the period of a total sympathetic block following thyroid feeding the oxygen consumption in ml. per square meter per minute was 136.5 cc., whereas the oxygen consumption in ml. per minute was 90 cc. Thus, although the actual average oxygen consumption in ml. per minute was lower, following rather than prior to thyroid feeding and during a total sympathetic block, the oxygen consumption in ml. per square meter per minute is higher than the same prefeeding control.

When the discrepancy in the oxygen consumption in ml. per square meter per minute, resulting from differences in the total body fat of euthyroid and of thyroid-fed animals, is taken into consideration, little or no significant difference could be seen in the oxygen consumption of euthyroid and thyroid-fed dogs during the maintenance of a total sympathetic block.

Effect of l-Epinephrine or of l-Norepinephrine Infusion. In euthyroid dogs, the calorigenic effects of *l*-epinephrine and of *l*-norepinephrine were quantitatively identical. When *l*-epinephrine or *l*-norepinephrine was infused intravenously into thyroid-fed animals, there was potentiation of their calorigenic effects which resulted in a significantly greater increase in the pulmonary oxygen uptake of the thyroid-fed animals, as contrasted with the euthyroid animals (fig. 12). As in the case of epinephrine and norepinephrine infusion in euthyroid dogs, the greater average increase in the oxygen consumption, produced by norepinephrine, can be accounted for in terms of molecular weight. Since the molecular weight of *l*-epinephrine is 8 per cent greater than that of norepinephrine, the infusion of these substances in equal metric weights should result in *l*-norepinephrine having approximately 8 per cent greater activity than *l*-epinephrine. This was the case.

Effect of Benzodioxane Injection during the

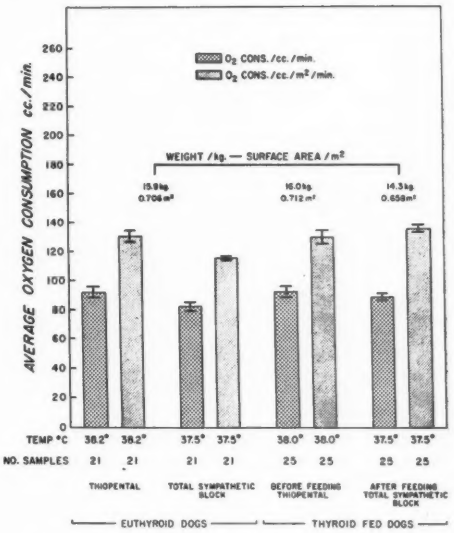

FIG. 13. Effects of a total sympathetic block on the average oxygen consumption in cubic centimeter per minute and in cubic centimeter per square meter per minute in euthyroid and thyroid-fed dogs under light Thiopental anesthesia, prior to surgical stimulation and following a total sympathetic block.

Infusion of l-Epinephrine or l-Norepinephrine. In contrast to the profound effects of benzodioxane on blood flow per minute, as reported above, it was found (tables 1 and 2)* that it has little significant effect upon the calorigenic activity of either *l*-epinephrine or *l*-norepinephrine during their infusion.

Lactate, Pyruvate and Glucose Concentrations

Thyroid Feeding. There was no change in the serum lactate, pyruvate or blood sugar concentrations of the thyroid-fed dogs, when their postfeeding levels, determined under light Thiopental sodium anesthesia, are compared with their prefeeding levels determined under similar circumstances. Following surgical stimulation in control determinations (fig. 14, tables 1 and 2),* the serum levels of lactate and pyruvate and blood sugar levels of the thyroid-fed dogs showed a small but significant increase as contrasted to the euthyroid dogs.

Effect of Total Sympathetic Block. There was

* See footnote p. 4.

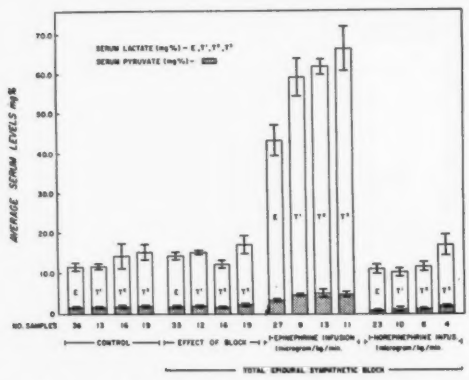

FIG. 14. Effect of thyroid feeding, total sympathetic block and the infusion of *l*-epinephrine or *l*-norepinephrine on the serum levels of lactate and pyruvate in the euthyroid and thyroid-fed dogs.

no significant change in the serum lactate and pyruvate concentrations following a total sympathetic block in any of the groups of dogs. The average serum lactate and pyruvate contrations increased slightly in the euthyroid dogs and in the dogs thyroid-fed for one- and three-weeks and decreased slightly below control values in the two-week thyroid-fed dogs (fig. 14). There was, however, a decrease in the blood sugar concentrations of all groups of dogs below their control values following a total epidural sympathetic block (tables 1 and 2).* There was no significant difference in the blood sugar determinations of all groups of dogs, following a total sympathetic block.

Infusion of l-Epinephrine and l-Norepinephrine

The infusion of *l*-epinephrine resulted in significant increases in the serum lactate and pyruvate levels in all groups of dogs, the increases being greater in the thyroid-fed dogs than in the euthyroid dogs. The infusion of *l*-epinephrine produced a significant increase in blood sugar in both euthyroid and thyroid-fed animals (fig. 14).

In contrast to the effects of *l*-epinephrine infusion upon the serum levels of lactate and pyruvate and the blood levels of sugar, the infusion of *l*-norepinephrine did not result in significant rises in the blood or serum concentrations of any of these metabolites. Rather, the infusion of *l*-norepinephrine resulted, in all groups of animals, in an average fall of serum concentrations of lactate, pyruvate and of the blood sugar concentration (fig. 14, tables 1 and 2)*. The serum pyruvate concentrations during norepinephrine infusion were significantly lower than prior to infusion. The decrease in the serum lactate and blood sugar concentrations were not statistically significant at the $p < .05$ level.

DISCUSSION

The technic of a total sympathetic block, either by the subarachnoid injection of a local anesthetic agent or by the use of intravenous ganglionic blocking agents (hexamethonium), has been demonstrated by clinicians to be capable of either preventing or abolishing the physiologic changes associated with thyrotoxic crisis or "storm."[29-34] Physiologists, interested in the mechanisms of action of the thyroid hormones, have failed to utilize similar technics in order to quantitate the role played by variations in epinephrine and norepinephrine activity in the physiologic effects observed in hyperthyroid man and laboratory animals. Isolated organ and tissue preparations have been used primarily. The slow rate of oxidation of the catechol amines in isolated organ or tissue preparations from hyperthyroid animals can be expected to result in a persistence in the activity of epinephrine and norepinephrine in such preparations for varying periods of time, following removal. The use of isolated organ or tissue preparations, therefore, does not necessarily separate the activity of the thyroid hormones from that of epinephrine and norepinephrine, as has been previously believed. Thus, the technic of a total sympathetic block, new to the laboratory investigation of the mode of action of the thyroid hormones though not new to the clinical treatment of thyrotoxicosis, has been used to analyze both the separate and combined effects of the thyroid hormones and of the sympathoadrenal hormones.

The occurrence of thyrotoxicosis in man, and the injection of *l*-thyroxine or the feeding of whole thyroid in both man and laboratory animals, has been shown to increase both the rate of metabolism of the body as a whole and

* See footnote p. 4.

the dynamic activity of the heart, in particular. The literature on hemodynamic and metabolic effects of hyperthyroidism in man and laboratory animals has been excellently reviewed by Raab,[14] Means,[50] Andrus[51] and Rasmussen.[52] The hemodynamic and metabolic changes, observed in the control state in our animals following thyroid feeding, are in agreement with the changes referred to or reported by the above authors.

The data presented above, together with a review of the literature, serve to emphasize two important points: (1) the hemodynamic and metabolic response to reflexly released, injected or infused epinephrine and norepinephrine may be increased by increased concentrations of the thyroid hormones and decreased or abolished in the hypothyroid state and (2) a total sympathetic block, in preventing the reflex release of epinephrine and norepinephrine, has diminished or abolished the metabolic and hemodynamic changes resulting from thyrotoxicosis, thyroxin injection or thyroid feeding in man and laboratory mammals.

In regard to the first point, the inotropic,[2] chronotropic,[1-8, 11, 12, 20, 21] calorigenic[1, 17, 18, 22, 24] and pressor[2, 5, 7] effects of adrenalin or of its components, epinephrine and norepinephrine, have been found to be increased in hyperthyroid man and animals. The glycogenolytic effects of adrenalin or of *l*-epinephrine[19, 23] are similarly increased by thyroid feeding or thyroxine injection. The data presented have demonstrated that the calorigenic effects of both epinephrine and of norepinephrine (fig. 12) are identical in euthyroid animals and equally increased in thyroid-fed animals. The chronotropic effects of both epinephrine and norepinephrine have been found to be increased in all groups of our thyroid-fed dogs (figs. 1, 3, 4). That there is an increase in the positive inotropic effects of both *l*-epinephrine and of *l*-norepinephrine in our dogs, as a result of thyroid feeding, is substantiated by the following:

(a) There was a significant increase in the effective right and left ventricular stroke work of the thyroid-fed dogs during the infusion of epinephrine and norepinephrine over the values observed in euthyroid dogs at similar rates of infusion (figs. 5–8). It has been made clear in the work of Sarnoff, Berglund and Case[44-48] that the functional capacity of ventricular heart muscle is best reflected in the relationship of right and left atrial mean pressures to the stroke works of the right and left ventricles, respectively. These workers have demonstrated that both epinephrine and norepinephrine, by virtue of their positive inotropic effects, increase the force of ventricular contraction and thus increase the right and left ventricular stroke work per unit of individual filling pressure.[44, 46] It has also been demonstrated that the positive inotropic effects of *l*-epinephrine and of *l*-norepinephrine in dog and in man are quantitatively identical.[43] In our series of euthyroid dogs, epinephrine and norepinephrine infusion produced equivalent increases in right and left ventricular stroke work per unit of right and left atrial mean pressure, respectively. In the thyroid-fed dogs, the infusion of both epinephrine and norepinephrine resulted in significantly greater increases in both right and left ventricular stroke work and significantly greater reductions in both right and left atrial mean pressures, than observed in the euthyroid dogs. (b) Benzodioxane was used to reduce and make the peripheral resistance comparable during the infusion of epinephrine and norepinephrine in both euthyroid and thyroid-fed dogs. It has been pointed out that, at fairly comparable resistances, the cardiac indices (figs. 3 and 4) and indices of right and left ventricular stroke work (figs. 9 and 10) of the thyroid-fed dogs remain well above those observed in the euthyroid dogs.

The increases in the cardiac indices and the decrease in the average mean femoral arterial pressures are uniformly greater following the injection of benzodioxane during epinephrine infusion, than during norepinephrine infusion. These changes are in agreement with the work of Johnson, Green and Lanier[42] who demonstrated that similar adrenergic blocking agents merely decreased or abolished the vasoconstrictor component of activity of *l*-norepinephrine, whereas they both blocked the vasoconstrictor component of activity of *l*-epinephrine and produced an active vasodilation.

Dose response curves have been constructed from the infusion of either *l*-epinephrine or *l*-norepinephrine in euthyroid dogs.[43] Rates of infusion were as follows: 0.25, 0.50, 1.0, 2.0, 4.0, 8.0, 16.0, and 32.0 μg. per kilogram per minute. These dose-response curves indicated that a near maximum physiologic response to both epinephrine and norepinephrine was obtained at an infusion rate of 1 μg. per kilogram per minute. The peak physiologic response occurred at 2 to 4 μg. per kilogram per minute. At infusion rates greater than 4 μg. per kilogram per minute, a progressive decrease in all parameters of physiologic activity of *l*-epinephrine and *l*-norepinephrine, was observed. The physiologic activity of *l*-epinephrine and of *l*-norepinephrine in thyroid-fed dogs was consistently greater at all dose levels than in the euthyroid dogs, the peak response occurring at the same dosages as in the euthyroid dogs. The infusion of 1 microgram per kilogram per minute of *l*-epinephrine and of *l*-norepinephrine produced greater physiologic responses than were observed in euthyroid dogs at much higher rates of infusion. On the basis of these observations, clear potentiation of the physiologic activity of epinephrine and norepinephrine by the thyroid hormones is evident.

The calorigenic effects of epinephrine and of norepinephrine have here been shown to be equivalent in euthyroid dogs and equally increased by thyroid feeding. There is, however, a fundamental difference in their effects upon liver and muscle glycogenolysis, as reflected in part by changes in the serum concentrations of lactate and pyruvate and blood sugar (fig. 14, tables 1 and 2).* Whereas *l*-epinephrine uniformly produced a significant rise in the serum concentrations of lactate, pyruvate and sugar, a consistent fall in the average serum concentrations of these metabolites resulted from the infusion of *l*-norepinephrine. It is thus clear, in view of the normal or near normal blood and serum concentrations of lactate, pyruvate and sugar observed in the thyroid-fed animals in the control state, that norepinephrine is probably the predominant mediator of the physiologic effects of thyrotoxicosis, as far as the activity of the sympathetic nervous system is concerned. If epinephrine were a predominant mediator, higher levels of lactate, pyruvate or sugar than were observed would be expected in the control state.

Von Euler,[53] in his classic studies, has identified norepinephrine as the primary substance contained in and released from the sympathetic nerve endings as the predominant mediator of the activity of the sympathetic nervous system. It is, thus, not surprising that norepinephrine should appear from our control observations as the sympathetic substance most nearly reproducing in every way the physiologic effects of thyrotoxicosis.

In regard to the second point, the total sympathetic block, by preventing the reflex release of epinephrine and norepinephrine, effectively abolished the physiologic changes that occur as a result of thyroid feeding. Following a total epidural preganglionic sympathetic block, there was a decrease in the oxygen consumption, heart rate, cardiac index and right and left ventricular stroke works of the thyroid-fed dogs to values observed in euthyroid dogs with a total sympathetic block. There was a similarly observed elevation of the right and left mean atrial pressures to comparable levels in both the euthyroid and the thyroid-fed dogs. When one uses the individual filling pressures and the stroke works of the right and left ventricles as indices of ventricular contractility, it is seen that the thyroid hormones per se have no observable effect upon the dynamics of ventricular contraction in the absence of epinephrine or norepinephrine. This fact is in sharp contrast to the increase ventricular contractility in the same animals during the infusion of either *l*-epinephrine or of *l*-norepinephrine.

It is also to be noted that the arteriovenous oxygen differences of the thyroid-fed dogs with a total sympathetic block are not significantly different from the average arteriovenous oxygen differences of the euthyroid animals. There are also no differences in the serum metabolite or electrolyte concentrations of the euthyroid or thyrotoxic dogs with a total sympathetic block.

The complete similarity of the hemodynamics

* See footnote p. 4.

and metabolism of the euthyroid and thyroid-fed dogs with a total sympathetic block does not only indicate the absence of a quantitatively significant direct effect of the thyroid hormones on these parameters, but also establishes a physiologic rationale for the use of a total sympathetic block in the treatment or prevention of thyrotoxic crisis and storm. Crile,[32] Maddox, Coller and Pedersen,[31] Rea,[30] Bartels and co-workers[33] and Knight [29] have reported that the production of a total sympathetic block by the use of high spinal anesthesia is effective in reducing to normal or near normal values the accelerated heart rate and elevated rectal temperature of hyperthyroid individuals during a thyrotoxic crisis. Crile and Knight[29, 32] similarly reported the use of high spinal anesthesia to prevent the occurrence of tachycardia, hypertension and hyperthermia in thyrotoxic individuals during surgery.

Although no data has been presented in this paper to bear directly upon the problem, it is important to mention that a review of the work of others indicates that the adrenal cortical steroids are essential to the integrity of the end-organ effects, resulting from the combined activity of the thyroid hormones and of *l*-epinephrine and of *l*-norepinephrine. The evidence that a dynamic interrelationship exists in the activity of the thyroid hormones, *l*-epinephrine and *l*-norepinephrine, and the adrenal cortical steroids comes from the following facts:

(1) Adrenal cortical hypertrophy and hyperplasia occur in thyroid-fed or thyroxine-injected laboratory animals;[54-57] similar adrenal cortical changes have been observed in the hyperthyroid human, although their occurrence is not uniformly seen. (2) Adrenal cortical atrophy occurs in hypothyroid animals.[54, 57, 58] (3) Adrenalectomy in the hyperthyroid animal results in a decrease in the oxygen consumption of the animal, which may be restored by the administration of adrenal cortical extract alone.[59] (4) Thyroid feeding or thyroxine injection in the adrenalectomized dog or in the Addisonian human results in an increase in the amounts of adrenal cortical steroids necessary to maintain life.[50, 60] (5) Survival time in untreated adrenalectomized animals is greatly shortened by previous thyroxine injection.[59, 61] (6) Exhaustion atrophy and vacuolization of the adrenal cortex occurs in humans who died, primarily from thyrotoxic crisis.[62, 63] A later paper will deal with these observations.

Variations Between Results Obtained Utilizing a Total Sympathetic Block and Results Obtained Using Denervated or Isolated Organs or Tissues

The following types of preparations have produced results which have led to the conclusion that the thyroid hormones per se directly influence heart rate, ventricular contractility and tissue oxygen consumption. They are presented to show the possible errors which may results from their use in attempting to isolate the activity of the thyroid hormones from that of epinephrine and of norepinephrine.

(1) *The Denervated Heart.* The denervated hearts in situ or the denervated transplanted heart of thyroid-fed or thyroxine-injected dogs continue to beat at an accelerated rate.[64, 65] This fact has been accepted as evidence that the increased heart rate was due not to sympathetic activity, but to the direct effects of the thyroid hormones. As Cannon[66] and Sawyer and Brown[4] have shown, the heart is perfused by adrenalin released from the adrenal medulla and from the liver, spleen and other organs, following sympathetic stimulation. Not only is the denervated heart not isolated from the activity of epinephrine and norepinephrine, but this preparation was used by Cannon in a classic technic to determine, by observational increases in the rate of the denervated heart, the quantitative release of adrenalin from the adrenal medulla and sympathetic nerve endings of cats in varying physiological states.

(2) *Bilateral Adrenalectomy.* The persistence of an elevated heart and metabolic rate in adrenalectomized thyroxine-injected animals, maintained with adrenal cortical extract,[59] has been presented as proof that the role of thyroxine in producing these effects is primary in nature. This is not valid since this preparation does not alter the concentrations of norepinephrine and epinephrine released from sympathetic nerve endings throughout the body.

(3) *The Isolated Heart-Lung Preparation and the Isolated Tissue Slice.* The heart-lung prepa-

rations taken from thyroxine-injected animals were found to beat, immediately after removal and preparation, at a rate faster than those removed from euthyroid animals.[20, 67, 68, 69] This difference in heart rate, immediately after removal, was advanced as evidence of the direct effects of thyroxine upon the heart. However, in the work of Priestley and associates,[65] protocols show that during a four-hour period, following removal of the hearts, there was a progressive fall in the heart rate so that, at the end of four hours, there was little difference in the heart rate of preparations taken from thyroxine-injected and euthyroid animals. The defects in this type of preparation in terms of isolating the activity of epinephrine and norepinephrine from that of the thyroid hormones are several: (a) heart muscle, as shown by Raab,[73] avidly takes up and retains epinephrine and norepinephrine and (b) it has been demonstrated that thyroxine will specifically inhibit the oxidation of epinephrine and norepinephrine.[13] Thyroxine, theoretically by virtue of substitution at the alpha carbon atom on its side chain, can inhibit the activity of amine oxidase and thereby decrease the rate of destruction of epinephrine and norepinephrine by oxidation and deamination. The demonstration of a significant decrease in the amine oxidase concentration in the liver and blood vessels of thyroxine-injected animals by Spinks and Burn[19] and Spinks[70] lends further support to these observations. Furthermore, it has been shown that thyroxine can inhibit the oxidation of epinephrine and norepinephrine to adenochrome and noradenochrome by a cytochrome-indophenol-oxidase system.[13] Thus, in the heart-lung preparation from a thyroid-fed or thyroxine-injected animal, effective concentrations of epinephrine and norepinephrine may be expected to persist for an appreciable period of time.

In reference to the use of isolated atriums or isolated tissue slices, the persistence of an increased rate of contraction or of an elevated qO_2 cannot be taken as an index of the isolated activity of the thyroid hormones. Hökfelt[71] has demonstrated that heart muscle slices, removed from the euthyroid animal and kept at room temperatures for 12 hours, show no appreciable change in the concentrations of epinephrine or of norepinephrine. In the case of other tissues, normal epinephrine and norepinephrine concentrations in the tissue slice persist for as long as 24 hours at room temperature. In contracting perfused heart muscle, a more rapid decline in the concentration of epinephrine and norepinephrine can be expected.

Hökfelt[71] and Goodall[72] have further demonstrated an increase in the norepinephrine concentration in the heart muscle of thyroxine injected rats and sheep. It is thus evident that greater concentrations of the catechol amines may persist and remain active for a longer period of time in tissues isolated from thyrotoxic animals than from euthyroid animals.

In summary, the above technics, purportedly indicating a direct action of the thyroid hormones, do not necessarily, for the reasons outlined, separate the activity of the thyroid hormones from those of epinephrine and of norepinephrine. The technic of a total sympathetic block in the intact thyroid-fed animal is better able to abolish effectively the activity of epinephrine and norepinephrine, both by preventing their reflex release and by leaving intact normal routes for the oxidation or excretion of the catechol-amines, keeping in mind that the destruction of epinephrine and norepinephrine may be significantly retarded in the thyroid-fed animal.

Summary

(1) Thirty-one dogs were made hyperthyroid by the feeding of 0.8 Gm. U.S.P. thyroid per kilogram of body weight per day for periods varying from 1 to 3 weeks. Twenty-seven euthyroid dogs were studied as controls. The serum protein-bound iodine concentrations of the euthyroid dogs averaged 1.7 μg per 100 cc. Following thyroid feeding, the following serum protein bound iodine concentrations were observed: 7 to 10 days, 16.6 per 100 cc.; 11 to 15 days, 18.1 per 100 cc.; and 18 to 22 days, 16.9 μg. per 100 cc.

(2) Thyroid feeding produced the classic hemodynamic and calorigenic effects of hyper-

thyroidism, including significant increases in the heart rate, oxygen consumption, cardiac index and effective ventricular stroke works.

(3) To differentiate between the effects of *l*-epinephrine and *l*-norepinephrine and those of the thyroid hormones, the reflex release of epinephrine was abolished in both euthyroid dogs and thyroid-fed dogs by the use of a total epidural preganglionic sympathetic block. The total sympathetic block was produced by the epidural injection of a 0.45 per cent procaine hydrochloride solution.

(4) The metabolic and hemodynamic effects of thyrotoxicosis could be abolished by preventing the reflex release of epinephrine and norepinephrine with a total sympathetic block. Studies done during a 1 to 4 period of total sympathetic block demonstrated that there was no significant difference in the oxygen consumption, cardiac indices, heart rates, average right or left atrial mean pressures, ventricular stroke works and arteriovenous oxygen differences of the thyroid fed dogs as contrasted to the euthyroid group of dogs.

(5) All parameters of activity of *l*-epinephrine and *l*-norepinephrine were found to be increased by increased concentrations of the thyroid hormones. The infusion, either of *l*-epinephrine or *l*-norepinephrine into thyroid-fed dogs with a total sympathetic block, resulted in a rise in the oxygen consumption, heart rate, cardiac index and ventricular stroke works per unit of filling pressure, significantly greater than that seen during infusion in a comparable series of euthyroid dogs.

(6) Whereas the infusion of *l*-epinephrine or *l*-norepinephrine in euthyroid or thyroid-fed animals resulted in equivalent inotropic, chronotropic or calorigenic effects, there was a fundamental difference in the glycogenolytic effects of *l*-epinephrine and of *l*-norepinephrine, as reflected in the blood and serum concentrations of lactate, pyruvate and sugar. Whereas the infusion of *l*-epinephrine consistently resulted in a rise in the serum lactate, pyruvate and blood sugar, the infusion of *l*-norepinephrine, despite its equal calorigenic effect, produced a fall in the blood and serum concentrations of lactate, pyruvate and sugar.

(7) The normal values of serum lactate, pyruvate and of blood sugar observed in the thyroid-fed animals in the control state suggest that *l*-norepinephrine is the predominant mediator of the physiologic effects of thyrotoxicosis, as far as the activity of the sympathetic nervous system is concerned.

(8) It is concluded that there is a dynamic interrelationship between the thyroid hormones and *l*-epinephrine and *l*-norepinephrine. The physiologic effects of thyrotoxicosis are not the result of the isolated action of the thyroid hormones per se but are due to the physiologic effects of *l*-epinephrine and of *l*-norepinephrine, as augmented by the thyroid hormones.

(9) Consideration of the work of others and unreported data from our laboratory indicate that optimal concentrations of the adrenal cortical steroids are essential in order that the dynamic activity of the hormones of the thyroid and sympathetic nervous system become manifest.

Acknowledgment

The authors wish to express their appreciation for the advice and counsel of Dr. Chester A. White, Dr. Claude A. Villee and Dr. John Stanbury. We are indebted to Mrs. Frances Ashodian and Miss Vivian Mays of the Protein-Bound Iodine Laboratory at the Massachusetts General Hospital, and to Mrs. Anne Hurley and Miss Anna Murphy for their assistance in this work.

Summario in Interlingua

Le effectos hemodynamic e metabolic de un bloco sympathic total e del infusion de *l*-epinephrina o *l*-norepinephrina esseva studiate in 27 canes euthyroide e in 31 canes a alimentation thyroide. Le alterationes physiologic producite per le augmentate concentrationes del hormones thyroide esseva abolite per prevenir le discarga reflexe de epinephrina e norepinephrina per medio de un bloco sympathic total. Il esseva constatate que le effectos inotropic, chronotropic, e calorigene de *l*-epinephrina e *l*-norepinephrina esseva accentuate per le alimentation thyroide. Nos conclude que il existe un relation dynamic inter le hormones thyroide e inter le hormones del medulla adrenal e le terminationes nervose sympathic. Le alterationes hemodynamic e metabolic de thyrotoxi-

cosis non resulta del activitate isolate de hormones thyroide; illos es plus tosto causate per le effectos physiologic de epinephrina e norepinephrina, augmentate per le hormones thyroide. Nostre studios indica que *l*-norepinephrina es le mediator predominante in le alterationes effectuate per le alimentation de thyroide.

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Electrocardiographic Changes During Hypothermia and Circulatory Occlusion

By Clarence E. Hicks, M.D., Malcolm C. McCord, M.D. and S. Gilbert Blount, Jr., M.D.

An analysis of the electrocardiograms from 25 patients during reduction of body temperature and total occlusion of circulation reveals marked abnormalities in conduction and rhythmicity. Hypothermia was accompanied by slowing of the heart rate, depression of intracardiac conductivity, and by inhibition of the normal centers of impulse formation with resultant atrial arrhythmias. Circulatory occlusion during hypothermia was associated with a high incidence of ventricular arrhythmias. Changes noted in electric activity of the myocardium tended to return to normal with release of occlusion and warming of the patient.

HYPOTHERMIA and circulatory occlusion are technics recently introduced to permit direct vision, open heart surgery. Observations under these conditions have revealed a high incidence of cardiac arrhythmias, with ventricular arrhythmias in particular constituting one of the major hazards of the procedure. The purpose of this paper is to describe the changes in electric activity of the heart occurring during hypothermia and circulatory occlusion.

Material and Methods

The 25 patients whose electrocardiograms were analyzed ranged in age from 3 months to 36 years. They represented one-third of the total patients undergoing cardiovascular surgery under hypothermia up to February 1955. These patients were selected for study only in that technically satisfactory electrocardiographic records were obtained throughout the procedure. Twenty-four of these patients had congenital cardiovascular disease. The lesions consisted of valvular or infundibular pulmonic stenosis in 13 patients, atrial septal defect in eight patients and ventricular septal defect in three patients. One patient, the oldest, had acquired heart disease consisting of syphilitic aortic insufficiency. Details of the technics of hypothermic cardiovascular surgery have been presented in previous reports from this Institution.[1-3] Standard lead II was employed and was constantly monitored by oscillographic observation. Frequent director-writer recordings were made throughout immersion and surgery, with continuous recording during the occlusion period. Anesthetic agents employed were ether, cyclopropane and Pentothal. Medications administered during surgery included curare, succinyl choline and prostigmine. The patients were hyperventilated throughout the operative procedure. Two of the patients were receiving digitalis and one quinidine at the time of surgery.

Results

The electrocardiographic changes observed during the hypothermia and circulatory occlusion are considered under the following categories.

Changes in Cardiac Rate

Progressive slowing of the cardiac rate occurred with decreasing body temperature. This relationship of cardiac rate to temperature is shown in figures 1 and 2. A steep decline in heart rate is demonstrated in both patients in the early phase of temperature reduction, with a more gradual slowing of rate with further decrease in temperature. The rate frequently increased abruptly, coincident with a change in cardiac rhythm, particularly atrial fibrillation; however, with persistence of the newly established rhythm the rate again gradually decreased with further temperature reduction.

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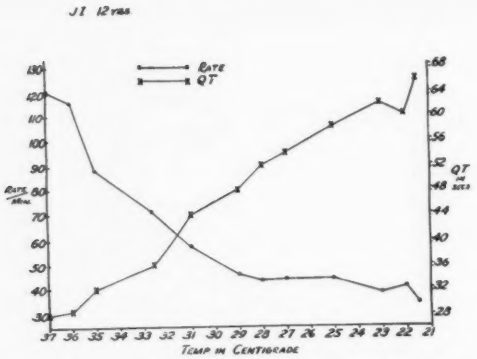

FIG. 1. The heart rate and Q-T interval are shown in relation to temperature during the preocclusion period of hypothermia in a 12 year old boy with a ventricular septal defect.

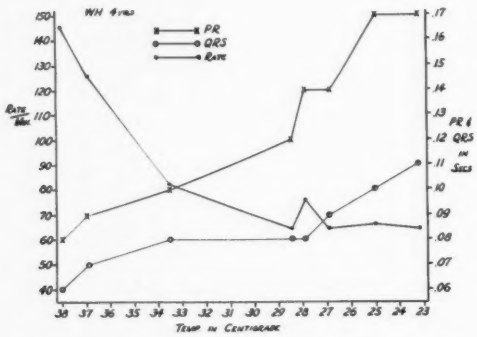

FIG. 2. The heart rate, P-R and QRS interval are shown in relation to decreasing temperature in a 4 year old boy with infundibular pulmonic stenosis.

Moderate increases in heart rate were noted following mechanical stimulation of the heart during manipulation. The addition of circulatory occlusion to the hypothermic state resulted in further slowing of the heart rate, frequently to the range of 10 to 20 beats per minute. Marked bradycardia often occurred during occlusion of circulation as is illustrated in line 2 of figure 6. An evaluation of the magnitude of the rate changes is afforded by consideration of the average rates in the 25 patients. Prior to immersion in ice water, the average heart rate was 122, prior to circulatory occlusion 55, and during occlusion 32 beats per minute. The heart rate progressively increased as the body temperature was returned toward normal.

Changes in Conduction Patterns

The P-R interval progressively increased with decreasing temperature levels and concomitant slowing of heart rate. This relationship of the P-R interval to temperature is demonstrated in figures 2 and 3. In figure 3 the P-R interval increased from 0.10 to 0.22 second during the temperature decrease, while the heart rate fell from 120 to 56 beats per minute. The QRS interval was considered in relation to temperature only during maintenance of a supraventricular pacemaker and showed progressive widening with decreasing temperature levels. The average increase in QRS duration in all patients was 72 per cent. The relation of the QRS time to temperature is shown graphically in figure 2. Figure 3 demonstrates the increasing QRS interval as it occurred in the electrocardiogram with a change from 0.05 second at 38 C. to 0.11 second at 23 C. The Q-T interval also widened with decreasing temperatures as is again shown in figures 1 and 3. This Q-T interval increase could not be solely attributed to slowing of the heart rate. A comparison of the Q-T interval to the R-R interval by means of Bazett's formula demonstrated an increasing C (constant) value with decreasing temperature levels.[4]

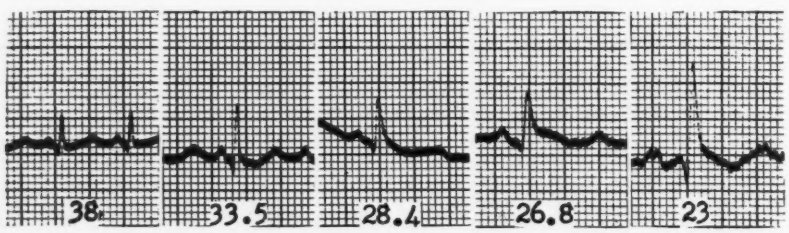

FIG. 3. Isolated complexes from the tracings of a 4 year old patient show P-R, QRS, and Q-T lengthening during stages of 15 C. temperature decrease. The numbers at the bottom of each panel are degrees centigrade.

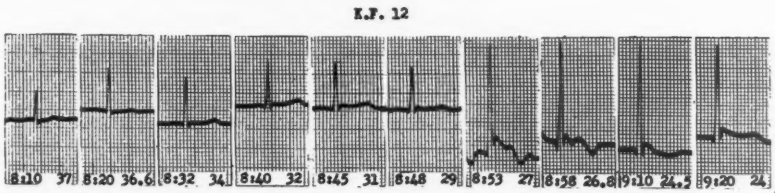

FIG. 4. The numbers at the bottom of each panel are: to the left, the time, and to the right the temperature in centigrade. From low and upright at the beginning the T waves invert at 27 C. then at 24 C, still prior to occlusion, they become upright again. QRS and Q-T lengthening, S-T segment deviation and the appearance of a prominent Q are shown in the tracings of this 12 year old patient.

Configuration Changes

The only consistent changes in the QRS were the appearance of a Q wave and the development of an R′ or notched R wave (fig. 4). The R′ or notched R appeared in 10 of the 25 cases. The amplitude of R and depth of S waves varied considerably but with no consistent pattern. There was a tendency to a decrease in QRS amplitudes during immersion. The amplitude and direction of the T waves changed frequently with no consistent pattern. Figure 4 illustrates T-wave inversion with return to the original upright pattern with no relation to surgical manipulation or interference with circulation. The S-T segments showed frequent displacement that could not be correlated with any single factor.

Alterations in Rhythm

A sinus mechanism was observed in all patients at the onset of the procedure. During the induction of anesthesia a supraventricular tachycardia frequently ensued which reverted to a sinus mechanism soon after cooling was begun. There then tended to be a progressive depression in the site of impulse formation with decreasing temperature. In 18 instances the first alteration in rhythm was the appearance of an ectopic atrial focus of impulse formation with a 1:1 atrioventricular response. The site of the pacemaker appeared to vary from the sinus node to an ectopic atrial focus or to a nodal focus. There was occasionally a constant ectopic focus in one of the previously mentioned sites but for convenience of grouping this is also included under the term wandering pacemaker. The temperature level at which a sinus rhythm was supplanted by a wandering pacemaker was related to the age of the patient. Younger patients maintained a sinus mechanism during a greater reduction of temperature than did older patients. A sinus rhythm was maintained throughout the entire preocclusion period of hypothermia in three patients under 8 years of age. In contrast, a wandering pacemaker replaced a sinus rhythm after less than 3 C. temperature decrease in three of the five patients over 15 years of age. This relationship of temperature, age and site of origin of impulse is shown diagrammatically in figure 5. The 7 month old infant, S. M., who showed a transition from sinus rhythm to nodal rhythm after only minimal temperature decrease had demonstrated a nodal rhythm at room tem-

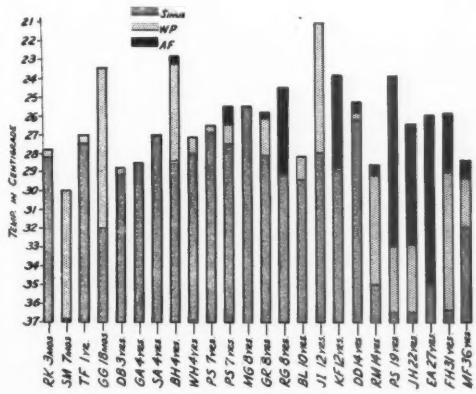

FIG. 5. The preocclusion rhythm changes are shown with the 25 patients arranged according to age. For simplicity three instances of atrial flutter and two instances of idioventricular rhythm were not included. Note particularly the rhythm changes with minor degrees of hypothermia in the older patients to the right and the persistence of sinus rhythm to low temperature levels in the younger patients to the left.

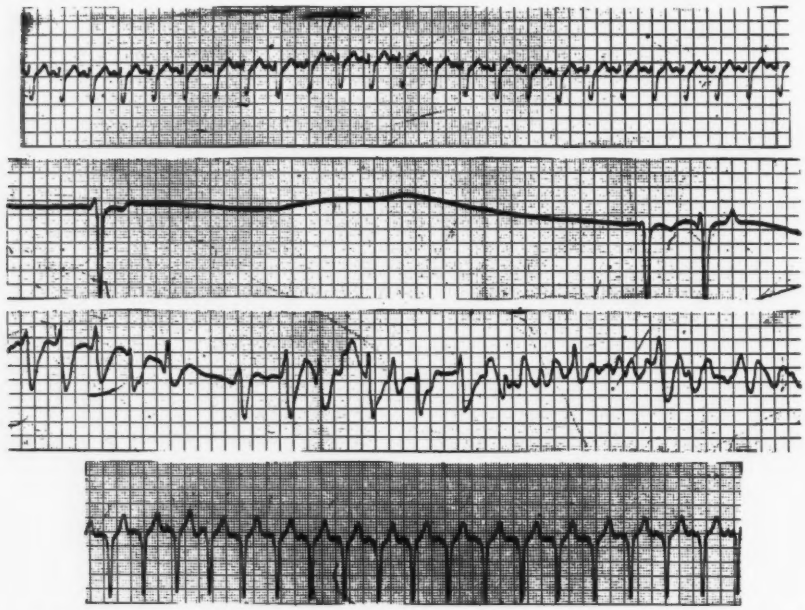

FIG. 6. These tracings are from a 4 year old patient. The first tracing is prior to occlusion, and the second tracing illustrates the long periods of standstill during circulatory occlusion. In the third tracing, also during occlusion, the onset of ventricular fibrillation is seen. The bottom tracing shows re-establishment of a sinus rhythm in the postcirculatory occlusion period.

perature on the day preceding surgery and thus represented no change in impulse mechanism by hypothermia.

The wandering pacemaker was supplanted by a rapid ectopic atrial focus consisting of atrial fibrillation in 12 patients and atrial flutter in three patients. A correlation was again afforded between the patient's age, the temperature level, and the occurrence of atrial fibrillation. Figure 5 demonstrates the appearance of atrial fibrillation predominantly in the older patients. A further depression in pacemaker to a ventricular level was observed in two patients prior to circulatory occlusion. This change was characterized by a regular ventricular rhythm, widening of the QRS time and further slowing of the rate.

Occlusion of circulation for a period varying from two to nine minutes was associated with marked alterations in the existing rhythms. Occlusion was accompanied by further changes in supraventricular rhythm consisting of a wandering pacemaker in three instances and atrial fibrillation or flutter in five instances. The striking abnormality in rhythm occurring during occlusion was the appearance of ventricular arrhythmias. Occlusion resulted in an idioventricular rhythm in 10 instances, cardiac standstill of 10 seconds or more in 13 instances and ventricular fibrillation in three instances. Examples of the type of idioventricular rhythms occurring during circulatory occlusion are presented in figures 6 and 7. Most of the patients demonstrating these rhythms had either considerable cardiac enlargement, cyanotic forms of congenital heart disease, or underwent surgical incision of the right ventricle. The ventricular rhythms occurring during circulatory occlusion were replaced by a supraventricular rhythm immediately following re-establishment of circulation in all but two patients. Operative deaths occurred in these two patients and were attributable to the arrhythmias per se.

Warming of the patient following the re-establishment of circulation resulted in changes in the pacemaker in the reverse order noted with decreasing temperature. A summary of

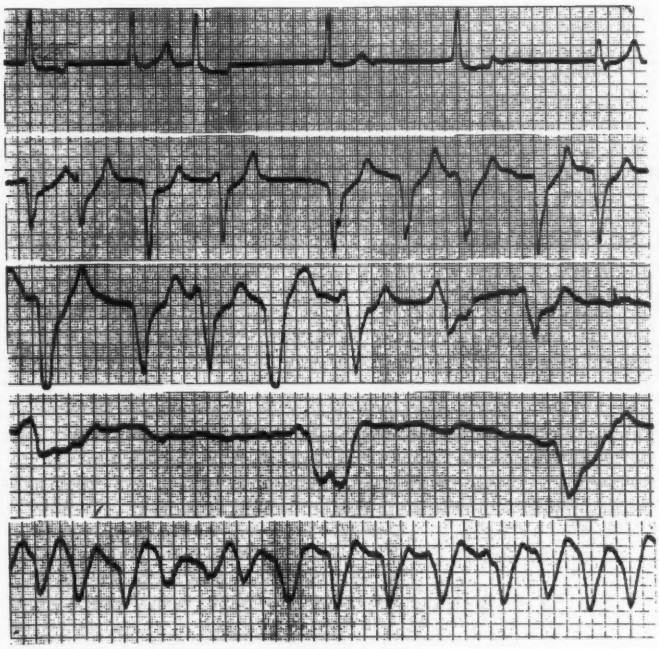

FIG. 7. Four panels recorded during an eight minute circulatory occlusion period at 27 C. in a 4 year old boy with a ventricular septal defect are shown. There was a return to sinus rhythm following re-establishment of circulation.

the preocclusion and occlusion rhythm changes is presented in table 1.

DISCUSSION

There have been many reports of electrocardiographic changes in animals during hibernation[5] or artificial hypothermia.[6-9] However, the electrocardiographic changes in humans during hypothermia have not been reported in significant numbers. The observations of the group of 25 patients reported at this time afford a basis for comparison with these previous studies in animals. Slowing of conduction and depression of higher centers of rhythmicity have been consistently reported by all observers in this field. The major difference that appears in the present study as compared with observations on animals is the severity of alterations in rhythms and the temperature levels at which they occur. Thus, atrial fibrillation occurs commonly in cooled adult human subjects but only rarely in cooled animals.

TABLE 1.—*Incidence of Arrhythmias*

	WP	A Fib.	A Flut.	IVR	VT	VF
Preocclusion	18	12	3	2	0	0
Occlusion	3	2	3	10	5	3
Totals	21	14	6	12	5	3

WP—wandering pacemaker, A Fib.—atrial fibrillation, A Flut.—atrial flutter, IVR—idioventricular rhythm, VT—ventricular tachycardia, VF—ventricular fibrillation.

Since the alterations in the electric activity of the heart constitute a major hazard of surgical procedures carried out under hypothermia and circulatory occlusion, an appraisal of the factors responsible for these changes is of critical importance. The slowing of heart rate with decreasing temperature is considered to result from a depression of the rhythmicity of the centers of impulse formation. Decreased total body metabolic activity may also contribute to this decreased heart rate. Electric conduction through specialized cardiac tissue

was consistently slowed with decreasing temperature and was manifest by an increase in the P-R, QRS, and Q-T intervals. This slowing is in accordance with the known effect of cold on the chronaxie of conduction tissues.[10] However, there are additional factors, particularly the potassium level, that may affect conductivity. Swan and associates[1] have shown in experimental animals and in a few patients in this series, that the serum potassium decreases and the pH rises during hypothermia. However, in the tracings analyzed in this study the T-wave configuration was quite variable, at times being very high and peaked and showing little resemblance to classic hypokalemic patterns. This lack of correlation with the potassium level is further supported by the report of Bigelow[11] who, found, using different technics of surgery, a Q-T prolongation with a rise in serum potassium. The widening of the Q-T interval described in our patients with decreasing temperature levels could also be attributed to the slowing in cardiac rate. However, calculation of the Q-Tc by means of Bazett's formula showed a progressive rise as temperature decreased. Thus the major factor resulting in depression of cardiac conductivity appears to be decreased temperature.

The progressive change in the location of cardiac impulse formation followed a similar sequence in all patients. There appeared to be a progressive inhibition of the higher centers of impulse formation with decreasing temperature. The rate of discharge of the sinus node was gradually decreased until rhythmicity was reduced below that of lower centers in atrial or nodal tissue. At this time the rhythm changed from a sinus mechanism to slower supraventricular rhythms with varying foci of impulse formation. To this point, the major effects of the cold were slowing of rhythmicity and conduction; however, with further reduction in temperature, atrial fibrillation or flutter supplanted the slow supraventricular rhythms. Atrial fibrillation was noted to begin with cardiac manipulation in some instances. The replacement of slowly discharging ectopic atrial foci by a rapid mechanism as atrial fibrillation or flutter presents a complex problem. This phenomenon may occasionally result from mechanical stimulation; however, it is considered in most instances to represent increased irritability of the atrial myocardium resulting from metabolic alterations related to decreased temperature. The studies by Penrod[12] and by Bing[13] on the ability of the hypothermic heart to extract oxygen suggest that hypoxia does not play a part in these rhythm changes.

Circulatory occlusion resulted in more profound disturbances of rhythm than those accompanying hypothermia alone. Only two patients exhibited ventricular rhythms prior to circulatory occlusion, suggesting that little ventricular irritability was produced by hypothermia alone. Eighteen additional instances of ventricular rhythms occurred during the period of circulatory occlusion and manipulation of the heart. It is considered that hypoxia of the ventricular myocardium, resulting from the total circulatory occlusion, increases the irritability of the ventricles and is the major factor leading to the development of ventricular arrhythmias. The incidence of ventricular rhythms has been shown to be decreased by the alkalosis resulting from hyperventilation and by the use of cholinergic agents such as prostigmine.[14]

The S-T segment deviations, QRS-configuration changes and T-wave changes did not follow a definite pattern. It was not possible to relate these changes to current of injury, hypoxia, cardiac manipulations or drug administration. The pattern of T-wave inversion with deep hypothermia as reported by Bigelow[11] and Hook[15] was not seen; however, the lowest temperature in the present series was 21.4 C.

Summary

An analysis is presented of the electrocardiographic changes recorded in 25 patients during reduction of body temperature and total occlusion of circulation. A wide range of abnormalities was noted in the electric activity of the myocardium under these circumstances. Many of these changes were inconstant and difficult to evaluate; however, there were certain electrocardiographic patterns that

appeared consistently in the majority of the patients. These dominant patterns are summarized as follows.

(1) Cardiac rate and conductivity as reflected by increased R-R, P-R, QRS and Q-T intervals were uniformly and progressively slowed with decreasing temperature.

(2) There was a progressive inhibition of higher centers of rhythmicity with decreasing temperature, with the lower centers of inherent rhythmicity assuming control of pacemaking activity as these higher centers were depressed. In two instances ventricular foci controlled the rhythmicity, thus representing complete depression of the higher centers of rhythmicity.

(3) The reduction of body temperature below a critical level, apparently related to the patient's age, resulted in an increase in the irritability of the atrial myocardium. Thus, atrial fibrillation or flutter was noted in 50 per cent of the patients in this series.

(4) Ventricular arrhythmias occurred infrequently during the period of temperature reduction. This low incidence of serious arrhythmias during hypothermia alone is considered to result from the production of alkalosis by hyperventilation and from the use of prostigmine.

(5) Ventricular arrhythmias frequently occurred during the period of total circulatory occlusion. Myocardial hypoxia and trauma incident to cardiac manipulation appear to be major factors responsible for the occurrence of these ventricular arrhythmias.

Summario in Interlingua

Es presentate un analyse del alterationes electrocardiographic registrate in 25 patientes durante reduction del temperatura corporee e occlusion total del circulation.

(1) Frequentia cardiac e conductivitate cardiac, in tanto que reflectite per le augmento del intervallos R-R, P-R, QRS, e Q-T, esseva uniforme- e progressivemente reducite con le reduction del temperatura corporee.

(2) Con le reduction del temperatura corporee il occurreva un progredente inhibition del centros superior de rhythmicitate. In tanto que le activitate de iste centros superior esseva deprimite, le centros inferior de rhythmicitate inherente usurpava le function de governar le rhythmo del corde. In duo casos, focos ventricular governava le rhythmo durante que le centros superior de rhythmicitate esseva completemente deprimite.

(3) Le reduction del temperatura corporee a infra un certe nivello critic—un nivello que esseva apparentemente relationate con le etate del patiente—resultava in un augmento del irritabilitate del myocardio auricular. Assi fibrillation o flutter auricular esseva notate in 50 pro cento del patientes de iste serie.

(4) Arrhythmias ventricular esseva de infrequente occurrentia durante le periodo del reduction del temperatura. On pote supponer que iste basse frequentia de serie arrhythmias durante hypothermia sol resulta del production de alkalose per hyperventilation e del uso de prostigmina.

(5) Arrhythmias ventricular esseva de frequente occurrentia durante le periodo de total occlusion circulatori. Il pare que hypoxia myocardial e trauma resultante del manipulation del corde es major factores in le production de iste arrhythmias ventricular.

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Dialyzable Currents of Injury in Potassium Intoxication Resembling Acute Myocardial Infarction or Pericarditis

By HAROLD D. LEVINE, M.D., SIDNEY H. WANZER, M.D. AND JOHN P. MERRILL, M.D.

A byproduct of experience with the artificial kidney was the detection of reversible electrocardiographic "currents of injury" in patients with electrolyte imbalance. These changes occurred irrespective of anatomic alterations and resembled the changes of acute pericarditis or myocardial infarction. The electrolyte basis for the "current of injury" was established by the prompt abolition of the RS-T segment elevations, when the electrolyte imbalance was corrected by means of artificial hemodialysis.

A REGULAR electrocardiographic feature of moderately advanced potassium intoxication is depression of the RS-T segments. The erroneous inference of myocardial infarction is generally avoided because of the direction of the RS-T shifts, the clinical setting in which this phenomenon is recorded and its association with other electrocardiographic abnormalities distinctive of potassium intoxication. In a few exceptional instances of potassium intoxication, however, elevation rather than depression of the RS-T segments may be produced. The resultant "currents of injury" may seem much more suggestive of acute myocardial infarction or pericarditis than potassium intoxication. In four such cases recently observed at the Peter Bent Brigham Hospital these changes could be wholly or partially eliminated by dialysis with the artificial kidney. Because of the practical and theoretical implications of this phenomenon these experiences are presented in some detail.

Case 1. J. C., a 40 year old electrician with acute renal failure due to carbon tetrachloride poisoning, was transferred to the Peter Bent Brigham Hospital after his electrocardiograms (fig. 1 *A*) had shown tall, peaked T waves characteristic of potassium intoxication. He gave no history of chest pain or compression. On examination the heart rate was 150, the cervical veins were distended, coarse bubbling rales were heard throughout the lung fields, a gallop rhythm was heard at the cardiac apex and the liver edge was felt two fingerbreadths below the right costal margin. Tracings recorded on the afternoon of admission showed sinus tachycardia (fig. 1 *B*), with left bundle branch block. The RS-T segments in leads V_1, V_2 and lead aV_R showed rather pronounced elevation, probably more than could be accounted for purely on the basis of left bundle branch block. Later in the afternoon the heart rate was 108 and the cardiac rhythm irregular and disturbed by runs of probable paroxysmal ventricular tachycardia. Over the right precordium the RS-T segment elevation was now more pronounced and associated with deep broad Q waves (fig. 1 *C*). The persistence of these changes was regarded as strong evidence for a "current of injury" and, it was believed, could not be attributed to left bundle branch block. At 6:40 p.m. hemodialysis was begun. At this time the serum potassium level was 7.8 mEq. per liter, sodium 127 mEq. per liter and the carbon dioxide content 9 mM per liter. Because the patient had marked pulmonary edema, the concentration of sodium in the bath fluid of the artificial kidney was maintained at 127 in order to avoid sodium loading in the presence of heart failure. The bath potassium concentration was initially set at 2 mEq. per liter but following the development of arrhythmia, was raised to 5. Two hours after the beginning of dialysis when the serum potassium level had fallen to 2.6 mEq. per liter and the sodium level had remained at 128 mEq. per liter, the electrocardiogram showed striking improvement. A supraventricular tachycardia (ventricular rate 210) had developed, the QRS complex had sharpened and shortened and the RS-T segment shifts over the right ventricle had almost disappeared (fig. 1 *D*). Though the patient improved temporarily after the dialysis

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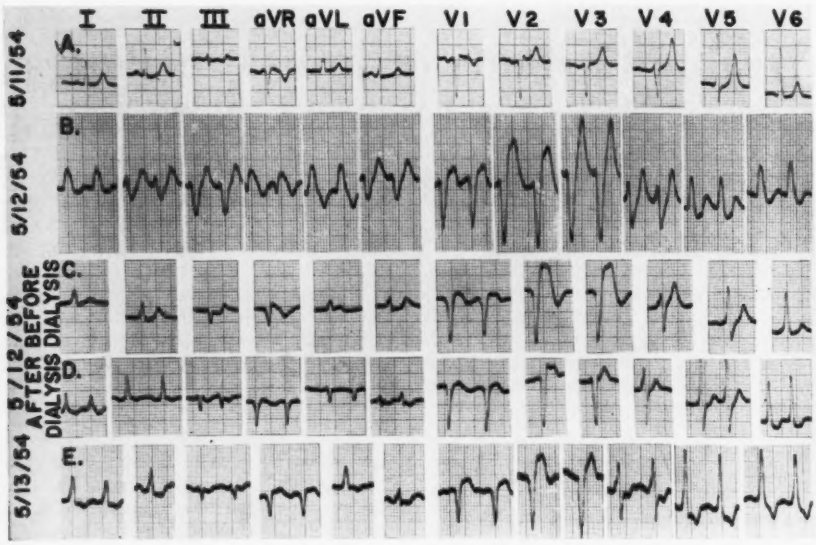

FIG. 1. *Potassium intoxication simulating acute myocardial infarction; partial elimination of electrocardiographic changes by artificial dialysis.* J. C. (case 1), a 40 year old man with acute renal shutdown. (*A*). Initial tracings characteristic of early potassium intoxication. (*B*). Tracings recorded on day of admission showing supraventricular tachycardia and left bundle branch block. (*C*). Tracings before dialysis show changes very suggestive of acute antero-septal myocardial infarct blended with those of moderately advanced potassium intoxication. (*D*). Almost complete recession of these changes after dialysis. (*E*). Partial return of changes on following day. Autopsy showed massive pulmonary embolism, moderate coronary sclerosis, thrombophlebitis and hypoxic nephrosis.

and even exhibited a moderate diuresis, on the following day he showed electrocardiographic (fig. 1 *E*), and on the succeeding day chemical (serum potassium 7.3 mEq. per liter) evidence of redeveloping potassium intoxication. On the afternoon of the third hospital day he suddenly sat up, complained of pain in the front of the chest, fell back gasping for air and died shortly thereafter. Postmortem examination showed massive pulmonary embolism, left femoral thrombophlebitis, marked renal tubular necrosis and moderate sclerosis of the coronary arteries. Meticulous examination showed no evidence of coronary thrombosis or myocardial infarction.

The rapid reversibility of the RS-T segment shifts here make it extremely unlikely that they were due to profound anatomic changes. It seems much more probable that these shifts resulted from chemical alterations. The acute pulmonary embolism was interpreted as a few days old and probably present when the electrocardiogram showed the unique features described above; and, hence could have accounted in part for the electrocardiographic changes described at that time.

Case 2. J. M., a 21 year old man developed acute renal failure following severe vertebral and abdominal injuries incurred in an automobile accident, associated with massive intraperitoneal hemorrhage and complicated by transfusion with incompatible blood. On admission his serum potassium level was 8.1 mEq. per liter, sodium 133 mEq. per liter, calcium 3.7 mEq. per liter and carbon dioxide 17.7 mM per liter. Electrocardiograms (fig. 2) were characteristic of acute potassium intoxication, showing atrioventricular and intraventricular block, peaked T waves and striking elevation of the RS-T segments in leads V_1 to V_3. At times there developed electrical alternans with alternation in the degree of elevation of the RS-T segments and in the direction of the T waves. The lowest strip in this figure shows a prolonged recording of this phenomenon. It is noteworthy that the T waves were upright when the RS-T "take-off" was higher and inverted when the RS-T "take-off" was lower. There was some variation in the amplitude of the QRS complexes but this was irregular and nonalternating. The respiratory rate was 24 and thus not an integral fraction of the heart rate (85). It seems reasonable, therefore, that this is a true example of electric alternans involving the T wave segment only, unrelated to cardiorespiratory synchronization. It was believed that though these tracings were com-

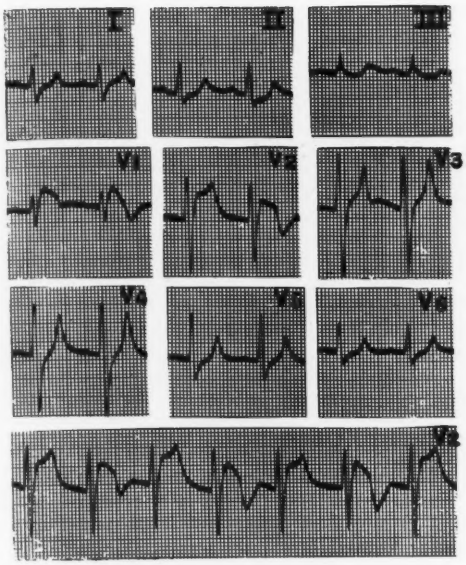

FIG. 2. *"Current of injury" over right precordium associated with right bundle branch block; electrical alternation of RS-T segments and T waves in potassium intoxication.* J. M., (case 2), a 21 year old man with acute renal shutdown. The tracings show intraventricular block and symmetrically peaked T waves. Electrical alternans demonstrated in leads V_1 and V_2, better illustrated in lower longer strip of lead V_2. The upward RS-T shift is not an expected feature of right bundle branch block. These changes suggest complicating pericarditis, acute cor pulmonale or anteroseptal ischemia.

patible with right bundle branch block, the RS-T segment elevation could not be explained on that basis. These changes receded after dialysis with the artificial kidney, but returned on the following day in more severe form.

Three days later his condition deteriorated and he was again dialyzed. Preceding dialysis, the electrocardiogram was again characteristic of potassium intoxication (fig. 3 *A*). The T waves were tall and peaked, the QRS duration was 0.11 second with incomplete right bundle branch block, and the RS-T segments were depressed in leads I, II and III and V_1 to V_6, elevated in leads V_1 and V_2. These changes resembled those of acute anteroseptal myocardial ischemia in the presence of right bundle branch block or possibly early infarction in the same area. Within 30 minutes after the start of the dialysis, the tracings showed improvement and at the end of the six hour run the electrocardiogram had returned to within normal limits (fig. 3, *B*), but the RS-T segments were still slightly elevated. There was corresponding clinical improvement.

Five days later, on July 2, 1954, a third dialysis was carried out because of the redevelopment of potassium intoxication with disorientation, tinnitus and blurring of vision. The electrocardiograms again showed peaked T waves, intraventricular block and pronounced elevation of the RS-T segments over the right precordium (fig. 4, *A*). As before, the changes reverted toward normal (fig. 4, *B*) as dialysis proceeded and the serum potassium value fell from 8.4 to 4.2 mEq. per liter. Because of continuing oliguria, dialysis was again necessary on July 10, 1954. Similar but less striking electrocardiographic changes were recorded before dialysis and disappeared thereafter. On the twenty-fourth day after his injury the patient entered the diuretic phase of his illness. His strength and sense of well-being gradually returned over a period of several weeks. Electrocardiographic tracings gradually became completely normal.

Case 3. J. W. G., a 50 year old contractor, was admitted on Oct. 31, 1950, with severe glomerulonephritis and uremia. A pericardial friction rub was

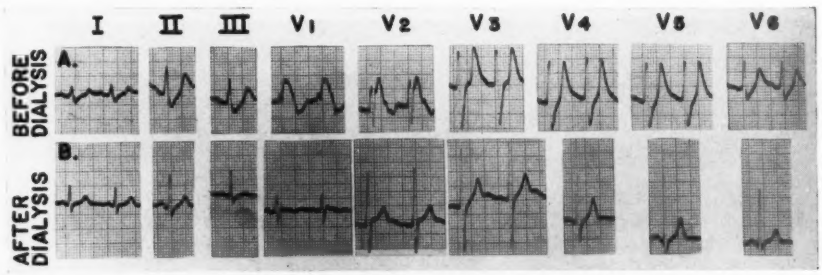

FIG. 3. *Extraction of RS-T shifts by artificial kidney.* Same patient three days later. (*A*). Tracings before dialysis showing intraventricular block, peaked T waves, depressed RS-T segments in leads II, III and V_4 through V_6, and elevated RS-T segment shifts in leads V_1 and V_2. Here the RS-T segment elevations over the right precordium may be reciprocal to RS-T segment depressions over the left precordium. (*B*). After 30 minutes of dialysis, tracings within normal limits. RS-T segments still slightly elevated.

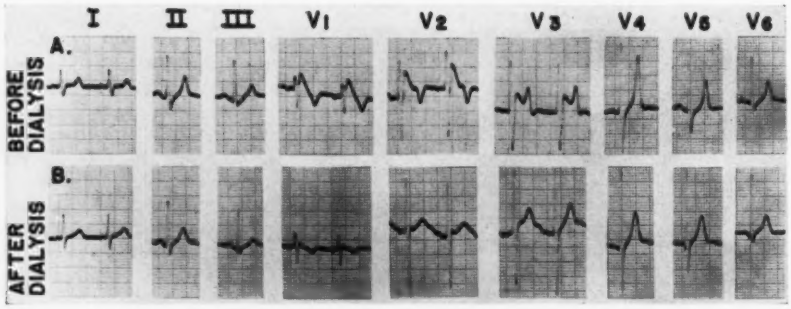

FIG. 4. *Duplication of same phenomenon in same patient; similar recession of RS-T segment shifts with dialysis.* Five days later. (*A*). Tracing on July 2, 1954, when serum potassium level was 8.4 mEq. per liter. At this time RS-T segment elevation over right precordium was not clearly a change reciprocal to RS-T segment depressions over the left precordium. (*B*). Tracings after dialysis show, coincident with fall of serum potassium to 4.2 mEq. per liter, almost complete disappearance of RS-T segment elevations. Patient recovered.

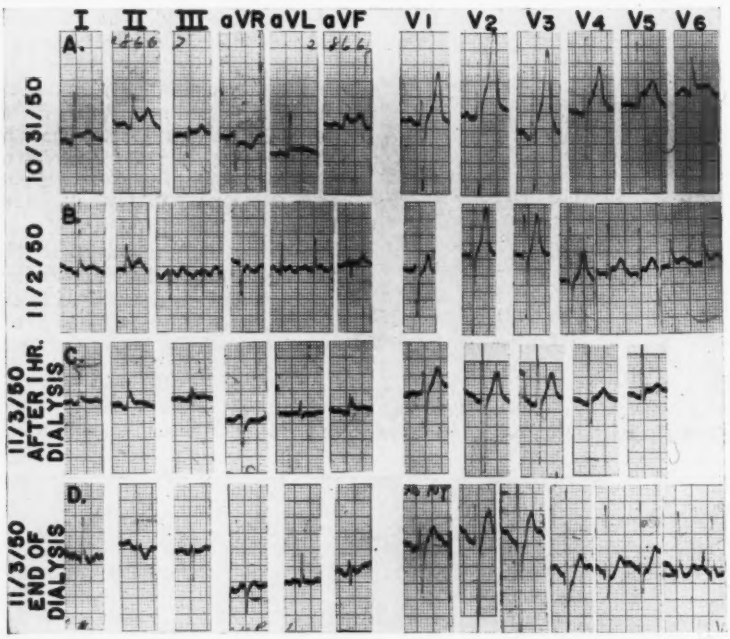

FIG. 5. *Dialysis eliminating changes of pericarditis and unmasking digitalis effect.* J. G., a 50 year old man with chronic nephritis and uremia. (*A*). Initial tracings showing changes compatible with early acute pericarditis (RS-T segment elevation in leads II, III, aV_F and V_1 through V_6). Tall peaked T waves suggest potassium intoxication. Serum potassium 5.2 mEq. per liter. (*B*). Two days later tracings show atrial flutter. Tracings on succeeding day, following digitalis therapy and before dialysis, show disappearance of flutter, no change in ventricular complexes. (*C*). Tracings following one hour of dialysis show decrease in T waves to normal amplitude, persistent but less pronounced RS-T shifts. (*D*). Tracings at end of dialysis show replacement of RS-T segment elevations by RS-T segment depressions suggesting digitalis effect. Autopsy showed fibrinous pericarditis, coronary sclerosis and myocardial fibrosis.

not heard. Electrocardiograms showed elevated RS-T segments in the left precordial leads characteristic of pericarditis (fig. 5, *A*). At the same time the T waves over the right precordium were tall and peaked, suggesting potassium intoxication. During this hospitalization the serum potassium level ranged from 3.8 to 5.2 mEq. per liter, the serum sodium ranged between 124 and 142 mEq. per liter but was usually low. Carbon dioxide varied from 10.3 to 21.1 mM per liter and was generally below normal. Two days after admission the tracings showed the development of auricular flutter (fig. 5, *B*); this arrhythmia disappeared when the patient was digitalized. On the following day the patient was treated with the artificial kidney. At the end of the first hour the peaked T waves had disappeared (fig. 5, *C*) but slight RS-T segment elevation persisted. However, five hours later, at the end of the dialysis, the RS-T segment elevation was replaced by RS-T segment depression (fig. 5, *D*), with a contour suggesting the effect of digitalis. The following blood chemistry values were determined immediately before and after the dialysis. Since the concentration of potassium in the bath fluid was 4 mEq. per liter there was relatively little change in the serum potassium as a result of the procedure.

	Before	After
Nonprotein nitrogen mg. %	256	152
Carbon dioxide mM/L	8.1	13.2
Chloride mEq./L	92	107
Sodium mEq./L	133	142
Potassium mEq./L	4.7	4.3

Following another dialysis the patient was discharged. He was hospitalized twice more because of further progression of his disease. He died on April 15, 1951. Postmortem examination showed chronic glomerulonephritis, fibrinous pericarditis, coronary arteriosclerosis and fibrosis of the myocardium especially involving the interventricular septum.

In this patient the electrocardiographic changes suggesting pericarditis were eliminated during the course of the dialysis. They were not seen again at any time in this patient. Fibrinous pericarditis was found at autopsy five and one half months after the illustrated sequence. In this case, acidosis rather than potassium intoxication may have been the

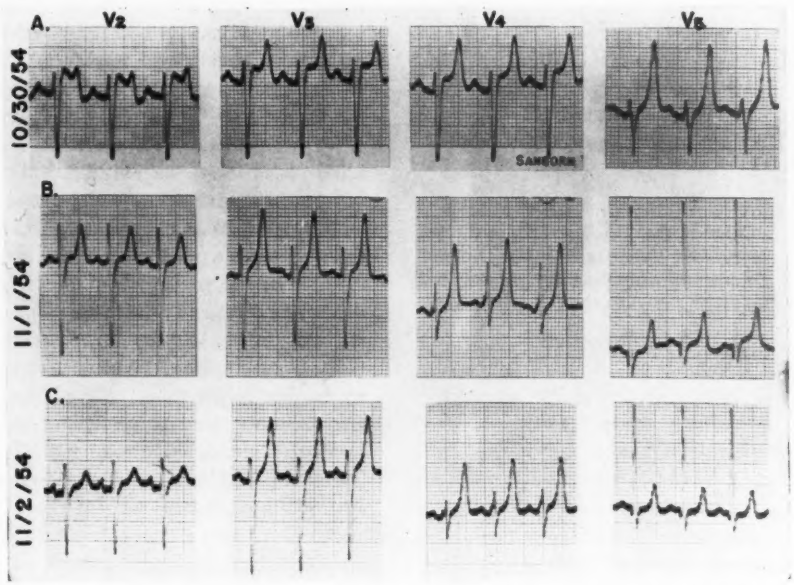

FIG. 6. *RS-T shifts of pericarditis washed out by artificial kidney.* L. G., a 19 year old soldier with acute renal failure and potassium intoxication (serum potassium 8.6 mEq. per liter). (*A*). Tracings (leads V_2 through V_5 only) show tall T waves, intraventricular block (probably right bundle branch block) and elevated RS-T segments in these leads. (*B*) Tracings after dialysis showing disappearance of all these changes excepting tall T waves, emergence of left ventricular hypertrophy. (*C*). Subsequent curves show tall T waves, no other electrocardiographic evidence of potassium intoxication. Postmortem examination showed fibrinous pericarditis, pulmonary infarcts and staphylococcus pneumonia and sepsis.

important chemical determinant. Whether the RS-T segment shifts reflected the anatomic changes in the pericardium or myocardium or were manifestations of electrolyte imbalance, the remarkable fact was their disappearance during the dialysis.

Case 4. L. O., a 19 year old soldier, sustained multiple fractures and soft tissue injuries in an automobile accident, followed by the development of acute renal failure for which he was transferred from an army hospital to the Peter Bent Brigham Hospital on Oct. 20, 1954. On admission his electrocardiogram showed tall, peaked T waves characteristic of potassium intoxication. During the early course of his hospital stay he was twice dialyzed, each time with marked subjective improvement, the second dialysis followed by electrocardiographic improvement as well. On Oct. 24 his electrocardiogram showed RR′ complexes in lead V_1 and sinus tachycardia (rate 110). On the following day tachypnea, tachycardia and a split second pulmonic sound were noted. These clinical and electrocardiographic findings justified the suspicion of acute pulmonary embolism. On October 27 he was again dialyzed; the T waves became lower and the RR′ complex in lead V_1 replaced by RS complex. On October 30 the patient's condition and his electrocardiograms indicated advancing potassium intoxication. His serum potassium level rose to 8.6 mEq. per liter and the electrocardiograms showed broader QRS complexes and taller T waves. On the day before his fourth dialysis (fig. 6, *A*), there were RR′ complexes and elevated RS-T segments in leads V_1 to V_4. This change persisted until the time of the dialysis. Tracings taken after the procedure (fig. 6, *B*) showed disappearance of these changes. They did not recur (fig. 6, *C*), although the peaked T waves continued. The dialysis resulted in the following chemical changes:

	Before	After
Blood urea nitrogen mg. %	290	165
Carbon dioxide mM/L	17.3	20.9
Chloride mEq./L	92.1	96.7
Sodium mEq./L	131	135
Potassium mEq./L	8.3	5.0

Three days later, amputation was performed at the junction of the upper third and lower two-thirds of the left leg. Within the next several days he had definitely entered into the diuretic phase of the kidney disease and he seemed to be recovering. But on November 10 he developed sepsis and pneumonia to which he succumbed within 24 hours. Postmortem examination showed staphylococcus septicemia and pneumonia, ischemic nephrosis, fibrinous pericarditis and multiple recent hemorrhagic infarcts of the lungs.

Discussion

Previous studies have demonstrated that depression of RS-T segments in certain of the precordial and limb leads and, frequently, elevation of the RS-T segments in lead aV_R are observed in moderately advanced potassium intoxication, and that these shifts may be eliminated by hemodialysis with the artificial kidney.[1, 2, 3] Some of the patients described in these earlier reports showed, as well, elevation of the RS-T segments in lead V_1 (figs. 2, 3, 5 and 9 of the first report,[1] fig. 3 of the second[2]) or in lead V_2 (fig. 4 of the third paper[3]). These changes were generally associated with intraventricular block. They were never widespread or profound enough to have suggested myocardial infarction or pericarditis but in the last case listed the possibility was suggested that they might be due to acute cor pulmonale. In one of a series of studies dealing with conditions that may be mistaken for myocardial infarction, Myers[4] presented a case of potassium intoxication which showed, in addition to the more usual manifestations, an apparent elevation of the RS-T junction and a cove-like RS-T segment and T wave in lead aV_L resembling that seen in myocardial infarction. Comparison with other leads, however, showed that this shift was recorded within, and was thus part of, a prolonged QRS complex; this change was thus referable to the conduction defect of potassium intoxication and not a sign of infarction. Following this lead, all tracings in the present series were re-examined to determine whether the RS-T segment shift was an apparent rather than real one and produced in a slurred prolonged QRS complex; but this possibility could not be confirmed in any of the cases here presented.

In cases 1 and 4 the sequence was somewhat muddied by the development of acute cor pulmonale which may conceivably have contributed, in part, to the electrocardiographic picture. RS-T segment elevation in the right precordial leads may develop as a reciprocal change to RS-T segment depression over the left precordium. This may occur in left bundle

branch block and may account for some (a small part, it is believed) of the RS-T segment elevation in leads V_1 to V_4 in case 1. But these RS-T segment shifts cannot be explained by the development of incomplete right bundle branch block such as was recorded in cases 2 and 4. There is nothing about right bundle branch block as such, complete or incomplete, which would be expected to result in elevation of the RS-T segments over the right precordium.

In some cases the sole electrocardiographic evidence of acute cor pulmonale may consist of inversion of the T waves over the right precordium, with, in rare instances, elevation of the RS-T segments in the same region. The possibility that the changes in cases 1, 2 and 4 are examples of this phenomenon seems extremely unlikely but cannot be denied categorically. But this would not explain the presence or distribution of RS-T segment shifts in case 3, which neither clinically nor pathologically presented evidence of acute cor pulmonale. Nor would it explain the rapid reversibility of these changes on dialysis in all four cases.

It has been demonstrated in the experimental animal that subendocardial injection of potassium salts results in RS-T segment depression in leads related to the overlying epicardium,[5, 6] while the subepicardial injection of potassium salts[5, 6] or their application to the pericardial surface[7] produces RS-T segment elevation in the same leads. There is no evidence that the blood perfusing the deeper layers of the ventricular wall has a different potassium content from that bathing the more superficial layers. From the fact that in moderately advanced potassium intoxication RS-T segment depression is generally recorded in the precordial leads and RS-T segment elevation in lead aV_R (to which, in general, more of the endocardial potentials are projected) and from the fact that block in the subendocardially located bundle branches may be recorded occasionally during the development of potassium intoxication, it was suggested, by exclusion, that this phenomenon may be explained by the greater vulnerability of the subendocardial laminae to the toxic effect of potassium.[2] This has not been proved.

One of the major struts of the science of electrocardiography has been electrocardiographic-pathologic correlation. For years electrocardiographers have sought vindication in the anatomic verification of their deductions from the electrocardiogram. The RS-T segment shifts of acute myocardial infarction and acute pericarditis, for example, are assumed to result from anatomic changes in the myocardium. At times electrocardiographic changes characteristic of either of these conditions are not associated with histologically demonstrated lesions. In explanation of this discrepancy, it has at times been averred that the lesion is still in its "biochemical phase"; the anatomic phase has not yet been attained. In the past such claims have been made rather loosely, on a priori grounds. But support for this attitude has recently been offered by the results of the new technics of histochemistry. The studies of succinic dehydrogenase activity by Wachstein and Meisel[8] and those of Yokoyamo and co-workers,[9] using a histochemical technic, demonstrated reduction in enzyme activity in the early hours after experimentally induced or spontaneous myocardial necrosis. This reduction in enzyme activity frequently extended to fibers which showed no significant changes with routine staining technics.

Another new technic is dialysis with the artificial kidney. This procedure was introduced as a practical approach to the correction, for longer or shorter periods of time, of certain abnormalities in body chemistry. The present series of observations with this technic raises certain theoretic questions. It seems reasonable that a change which can be eliminated by dialysis should be considered a chemical change. Would this same reasoning apply to a dialyzable "current of injury?" And should not these changes be considered chemical in origin, whether or not they are associated with anatomically demonstrable changes? A demonstration that electrocardiographic changes of this type, occurring in proved myocardial infarction or pericarditis in the absence of electrolyte imbalance, can similarly be reversed

rapidly on chemical manipulation, would be of profound interest. We know of no observations on the effect of artificial hemodialysis upon these electrocardiographic phenomena.

Summary and Conclusions

Four patients with potassium intoxication associated with acute or chronic renal failure showed RS-T segment elevations over the right or left side of the precordium, resembling that occurring in acute myocardial infarction or pericarditis. One patient survived. The three fatal and autopsied cases (cases 1, 3 and 4) showed at postmortem examination pulmonary embolism (cases 1 and 4), fibrinous pericarditis (cases 3 and 4) or coronary artery disease with myocardial fibrosis (case 3) or without it (case 1); none showed fresh myocardial infarction. Regardless of this complicated anatomic substrate, it was possible in all four cases specifically to eliminate this "current of injury" entirely or, in large part, by artificial hemodialysis with the artificial kidney. This emphasizes the ultimate chemical origin of these changes, whether or not associated with anatomic changes.

In dealing with patients with potassium intoxication the possibility of confusion with acute myocardial infarction should be borne in mind.

Summario in Interlingua

Quatro patientes con intoxication a kalium associate con acute o chronic disfallimento renal monstrava supra le dextere o sinistre latere del precordio elevationes del segmento RS-T que esseva simile a illos occurrente in acute infarcimento myocardial o in pericarditis. Un del patientes superviveva. Le tres casos mortal (casos 1, 3, 4) esseva autopsiate e monstrava embolismo pulmonar (casos 1, 4), pericarditis fibrinose (casos 3, 4), o morbo del arteria coronari, con fibrosis myocardial (caso 3) o sin illo (caso 1). Nulle de iste casos monstrava recente infarcimento myocardial. In despecto de iste complexe substrato anatomic, il esseva possibile in omne quatro casos eliminar iste "currente de lesion" completemente o extensemente per medio de hemodialyse artificial in le ren artificial. Iste facto sublinea le origine ultimemente chimic del alterationes sub discussion, si o non illos es associate con alterationes anatomic.

In casos de patientes qui monstra intoxication a kalium, on debe considerar le possibilitate de un confusion con acute infarcimento myocardial.

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Occlusion of a Renal Artery as a Cause of Hypertension

By EUGENE F. POUTASSE, M.D.

This paper presents three cases and the summary of a fourth case, in which occlusion of a renal artery was the cause of hypertension. Three patients were relieved of hypertension by nephrectomy. The literature on nonembolic renal artery occlusion with hypertension is reviewed, including 21 autopsy reports and 16 cases in which the patients were relieved of hypertension by nephrectomy or thromboendarterectomy. When a patient is found to have renal hypertension, the possibility of renal artery occlusion should be considered. Translumbar aortography currently is the best means of demonstrating renal artery occlusion.

SINCE Goldblatt[1] demonstrated in 1934 that compression of one or both renal arteries with a metal clamp will produce hypertension in dogs, the clinical implications of experimental hypertension have been extensively explored. It is now generally accepted that a causal relationship exists between various lesions of the kidneys and hypertension in human beings. Unfortunately, the term "Goldblatt phenomenon" has been loosely applied to many clinical and pathologic conditions which do not simulate the state experimentally elicited by application of an arterial clamp.

Several recent reports have described patients with obstructive lesions of one or both main renal arteries who exhibited the syndrome of malignant hypertension and in whom the arterial occlusion seems to have preceded the onset of hypertension. Such cases represent a close parallel to experimental renal arterial hypertension. Correlation of clinical data with pathologic findings has facilitated accurate diagnosis of this type of renal hypertension and has clarified the urgent indications for early definitive treatment.

This paper presents reports of three patients who had renal hypertension and clinical and pathologic evidences of occlusion of one main renal artery or a major branch. Each of these patients was relieved of hypertension following nephrectomy. A fourth case, previously reported by Fisher and Corcoran,[2] is presented in summary. The aim is to emphasize the significance of renal artery occlusion as a cause of hypertension and to describe the recognition and treatment of this condition, with special emphasis on the value of aortography in demonstrating the lesion.

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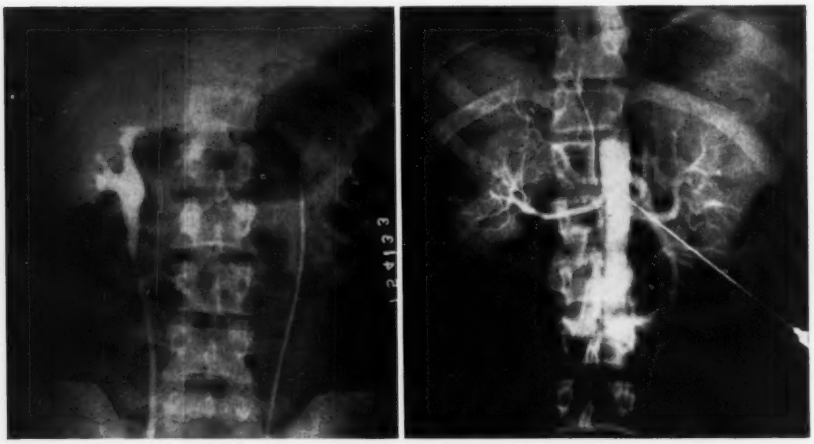
CASE REPORTS

Case 1. In December 1952, R. V. S., a 30 year old white man, suddenly developed right loin pain that persisted for five days. An intravenous urogram revealed a nonfunctioning right and a normal left kidney. No opaque calculi were seen along the urinary tract. Four days later a second intravenous urogram showed prompt excretory function of both kidneys, although there was poor concentration of contrast medium in the right kidney. The urinalysis was negative for sediment and albumin. Blood pressure was not recorded at that time.

Four months later, the blood pressure was slightly elevated with a systolic of 146. A month later the blood pressure was 240/140 and the patient complained of frequent morning headaches. There was no family history of hypertension.

A month later, the blood pressure was 180/130 and the patient had lost 12 pounds in weight. The fundi showed generalized moderate angiospasm. The blood urea nitrogen content was 10 mg. per 100 ml.; urea clearance was 95 per cent of average normal. Urine culture produced *Escherichia coli* and streptococcus. Another intravenous urogram was interpreted as showing good bilateral excretory function. Retrograde pyelograms demonstrated a normal left kidney but gave indication of an abnormality of the lower pole of the right kidney. Indigo-carmine excretion from the right kidney was diminished as compared to that of the left.

The patient was referred to us in June 1953, by Dr. A. K. Hamp of Grand Rapids, Mich., who made the tentative diagnosis of renal hypertension and furnished relevant clinical data. On examination here, the blood pressure was 165/120 and the fundi revealed grade I constriction of vessels. The urea



A *B*

FIG. 1. Case 1. (*A*) Retrograde pyelogram of right kidney reveals small, compact lower calyces. (*B*) Translumbar aortogram demonstrates absence of branch of main renal artery to lower pole of right kidney. Zone of atrophy is sharply demarcated. Left renal artery and kidney are normal.

clearance was 100 per cent of normal in the first and 82 per cent in the second hour. An Addis test showed a volume of 610 cc.; maximum specific gravity of 1.015; and protein content of 0.7 Gm. per 24 hours. The sediment contained 1,200,000 red blood cells, 30,000,000 white and epithelial cells, and 102,000 casts in 12 hours.

The pyelographic abnormality was interpreted as a decrease in size and crowding together of the calyces in the lower pole of the right kidney (fig. 1*A*). A lesion of the renal artery was suspected; a translumbar aortogram (fig. 1*B*) demonstrated a narrow right renal artery. Arterial supply of the upper two thirds of the right kidney appeared normal but there was no filling of the arteries of the lower pole. The left renal artery and its branches appeared normal. These findings were attributed to occlusion of the artery to the lower pole of the right kidney with ischemia* of this area; nephrectomy was advised. The patient returned home for nephrectomy which was performed by Dr. J. A. Ryan on June 17, 1953, at the Blodgett Memorial Hospital, Grand Rapids, Mich.

Five months postoperatively, the blood pressure was 114/76 and the patient was entirely well. Eighteen months later, the blood pressure still was reported to be normal.

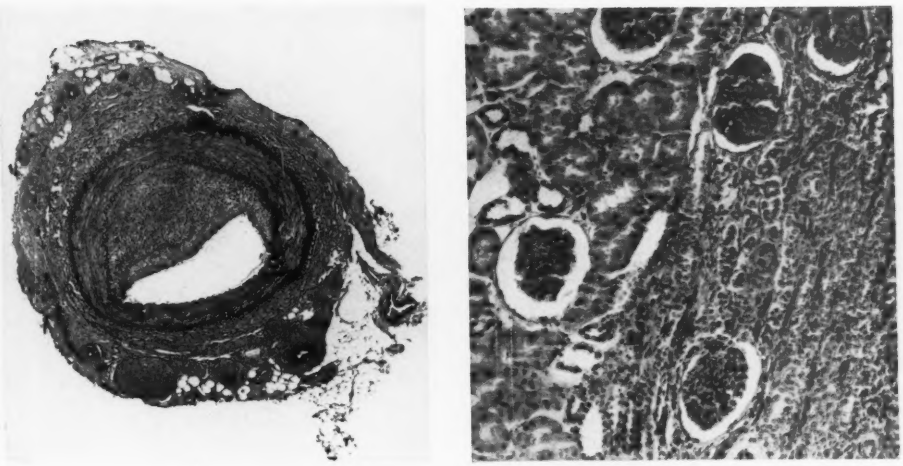
Pathology. The kidney was reported to show a clearly demarcated pale and ischemic lower pole. The major branch of the renal artery to the lower pole was partly occluded; the arteries to the remainder of the kidney appeared normal.

Slides were sent by Dr. C. A. Payne of the Blodgett Memorial Hospital, Grand Rapids, Michigan, and were reviewed by Dr. L. J. McCormack of our Department of Pathology. The artery to the upper part of the kidney appeared normal with a thin intima and normal elastic lamina and muscular coat. The lumen of the artery to the lower pole (fig. 2*A*) was approximately 70 per cent occluded by a mass of loosely arranged fibrous tissue covered by endothelium. The internal elastic lamina was intact and the muscular layer and outer elastic lamina were normal. On longitudinal section, the mass of collagenous tissue was partly recanalized by endothelial-lined vascular channels. Sections of the kidney demonstrated two distinct histologic features: (1) The upper part of the kidney showed normal renal parenchyma (fig. 2*B*); blood vessels entering the glomeruli appeared slightly thickened. (2) A junction line was present, which divided the normal parenchyma from an area in which the tubules were collapsed and atrophic, with slight increase of interstitial tissue, and in which the glomeruli appeared shrunken and showed a slight increase in tuft thickness.

The pathologic diagnosis was old, partial occlusion of lower secondary branch of the main right renal artery due to fibrous tissue, with renal atrophy distal to the occlusion.

Comment: This case is an example of renal hypertension caused by a partially ischemic kidney. It is believed that the initial vascular injury occurred at the time of the abdominal pain. Translumbar aortography five months later clearly demonstrated obstruction of the

* The term "ischemia" is used in this paper to indicate a decrease in arterial circulation as shown by aortography.



A *B*

FIG. 2. Case 1. (*A*) Cross section of artery to lower pole, showing partial obstruction of lumen (×20). (*B*) Photomicrograph of lower pole of kidney showing demarcation between the normal renal parenchyma on left and the zone of atrophy on the right (×110).

lower main branch of the right renal artery and nephrectomy was advised. The fact that the patient has remained normotensive for 18 months after nephrectomy is reasonable evidence that the arterial occlusion with resultant partial renal ischemia was the cause of the hypertension.

Case 2. W. J. J., a 52 year old white man, developed acute appendicitis in May 1954; a suppurative appendix was removed at operation. Recovery was complicated by ileus and evisceration. During his hospitalization the blood pressure was found to be elevated and albumin was detected in the urine. One month after discharge from the hospital he developed headaches, blurring of vision, nausea, vomiting, and nocturia. He had lost 35 pounds in weight. He was referred here on July 13, 1954, by Dr. Meyer Bloom of Johnstown, Pa., who had made a tentative diagnosis of renal hypertension.

The patient had been examined here in 1950 for episodes of syncope diagnosed as postural hypotension. The blood pressure at that time was 105/70 in the supine position. In late 1953, a hemorrhoidectomy was performed and the blood pressure was reported to be slightly elevated. There was no family history of hypertension.

The blood pressure was 178/118. The fundi showed grade II constriction and sclerosis of retinal arterioles, numerous hemorrhages and exudates and about 3 diopters of papilledema. The heart was enlarged to the left but the sounds were normal. Peripheral arterial pulsations were normal. Slight ankle edema was present; the liver edge was 3.5 cm. below the right costal margin.

The blood urea was 27, creatinine 1.0, and cholesterol 343 mg. per 100 ml. Urea clearance was 44 per cent of normal during the first and 37 per cent during the second hour. Urinalysis revealed 1 plus albuminuria, 2 to 5 red blood cells and a rare white blood cell per high-power field. Three urine cultures were sterile. Over a 10-day period, daily urinary protein excretion varied between 6.5 and 21.6 Gm. per 24 hours.

The electrocardiogram showed myocardial changes. By the Ungerleider-Gubner scale, the heart was calculated to be 6 per cent over normal size for the patient's height and weight. Tiselius electrophoretic analysis of the plasma proteins revealed a total protein content of 4.38 Gm. per 100 ml., with 2.19 Gm. of albumin, 0.73 Gm. of α-globulin, 1 Gm. of β-globulin and 0.46 Gm. of γ-globulin.

Examinations of the urinary sediment on several occasions revealed 62,000 to 390,000 casts, 2,320,000 to more than 18,000,000 red blood cells, and 880,000 to more than 16,000,000 white blood cells per 12 hours. Cold pressor and Regitine tests were negative. The averages of 44 blood pressure recordings over a one-week period were 172/117 in the supine position and 166/117 mm. Hg in the standing position.

The intravenous urogram revealed a normal right kidney with good excretory function, but only a faint trace of dye was seen in the tip of the lower calyx of the left kidney (fig. 3*A*). A left retrograde pyelogram demonstrated normal renal pelvis and calyces with slight reduction in size of the kidney

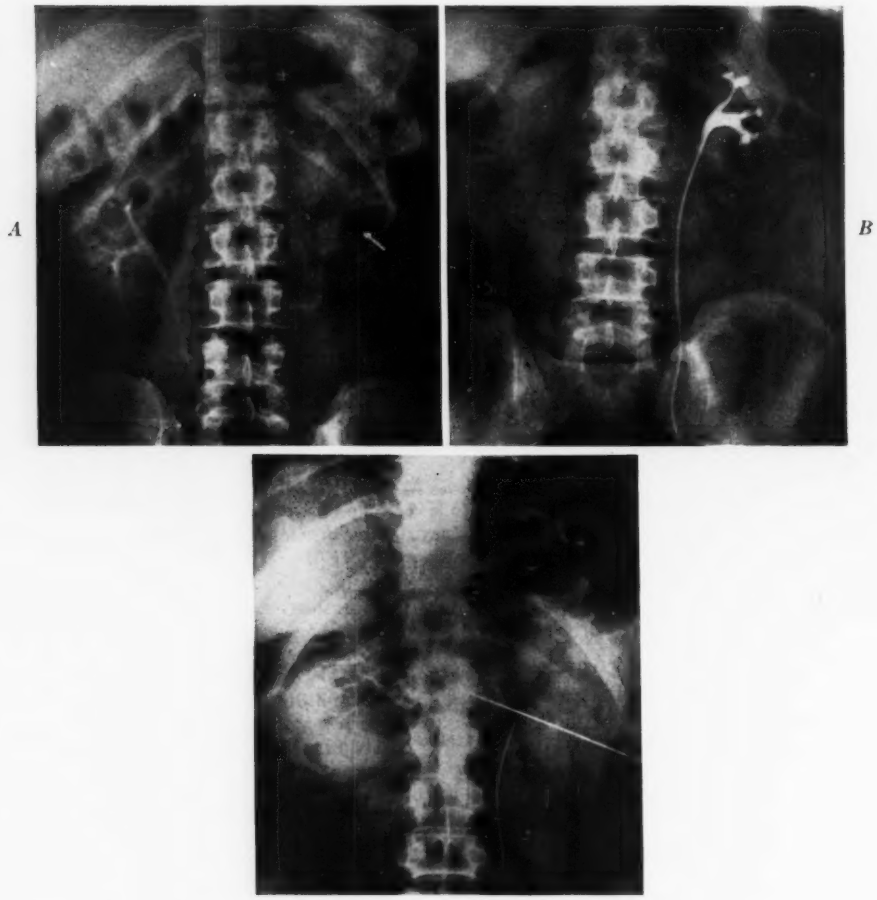


FIG. 3. Case 2. (*A*) Intravenous urogram reveals a trace of opaque medium in tip of lower calyx of left kidney, marked by an arrow. Right kidney is normal. (*B*) Retrograde pyelogram of left kidney; only slight diminution in size is evident. (*C*) Translumbar aortogram demonstrates absence of left main renal artery. A small aberrant renal artery, visible beside the needle, extends from the aorta to the lower pole. Right renal vascular system appears normal.

(fig. 3*B*). Intravenously injected indigo-carmine appeared after 13 minutes in poor concentration from the left ureteral catheter. Translumbar aortogram showed only a small aberrant renal artery to the lower pole of the left kidney (fig. 3*C*); the left main renal artery was not visualized. The arterial distribution to the right kidney was normal. The left renal artery was considered to be completely occluded. This was believed to be the cause of his malignant hypertension. Left nephrectomy was performed on July 30, 1954. The main left renal artery was pulseless and occluded by a hard plaque midway between the aorta and the kidney.

On the day following operation, the blood pressure was 129/86, supine. Rapid, progressive improvement of the retinopathy occurred with absorption of hemorrhages, exudates, and papilledema.

Three months later he was feeling well; blood pressure was 130/88. The proteinuria varied between 5 and 9 Gm. per 24 hours, on three occasions. A mannitol-para-aminohippurate renal clearance test indicated a renal blood flow of 537, renal plasma flow of 317, and glomerular filtration rate of 36.7 ml. per minute with filtration fraction of 0.12; the respective preoperative values were 293, 176, 46, and 0.27.

Seven months later he was asymptomatic and the blood pressure was 130/85. The fundi had be-

ome completely normal; proteinuria had diminished to about 1.5 Gm. per 24 hours.

Pathology. The left kidney (fig. 4) weighed 120 Gm.; its capsule stripped easily, revealing a smooth surface. The cut surface was uniformly blue-pink in color, except the lower pole where the cortex was pale. A hard clot, 1 cm. in length and 0.5 cm. in diameter, was visible and palpable in the main renal artery, completely occluding its lumen. A small patent aberrant renal artery led to the lower pole of the kidney. The renal veins and ureter were normal.

The microscopic pathologic description was prepared by Dr. J. B. Hazard of our Department of Pathology. Sections of the renal artery showed the lumen to be filled by blood clot, sufficiently old in the center to show complete loss of red-cell structure. No canalization was evident. The vascular wall was thin and distended by the clot. The internal elastic membrane and muscular layer appeared normal, except for moderate infiltration of lymphocytes and plasma cells, more evident in the adventitia.

Sections of the cortex from the upper pole showed areas of increased interstitial tissue with reduction in tubular tissue. Some of the tubules were dilated and contained granular coagula and hyaline casts. In the areas with greatest increase in connective tissue, the tubules that were present had a small caliber; and in such zones proximal, convoluted tubular epithelium could not be identified. Bands of well-preserved tubules were scattered throughout the kidney; no colloid-filled tubules were seen. The glomeruli were of normal size and their capillaries contained blood in the majority of tufts. A rare sclerosed glomerulus was present. The arcuate and larger vessels showed a moderate degree of intimal thickening.

The pathologic diagnosis was occlusion of main renal artery by partly organized old blood clot (thrombus), with focal atrophy of the cortical tubules and moderate arteriosclerosis of intrarenal arteries.

Comment: In this case it is likely that thrombosis occurred during the patient's convalescence from appendectomy. Within two months he showed evidence of rapidly progressive hypertensive vascular disease with grade IV eye-ground changes, depression of renal function, cardiac enlargement and a mean resting blood pressure of 176/117. Intravenous urography revealed that only the lower part of the left kidney retained any function. Translumbar aortography demonstrated that the main left renal artery was blocked, but that there was a small patent aberrant artery to the lower pole of the left kidney. Since nephrectomy, he has regained his health and has remained normotensive; eye grounds have become normal and renal function has steadily improved, indicating regression of the hypertensive vascular disease. The left renal artery was completely occluded by a thrombus. The kidney showed ischemic tubular atrophy; it is of interest that the intrarenal arteries showed only moderate intimal thickening.

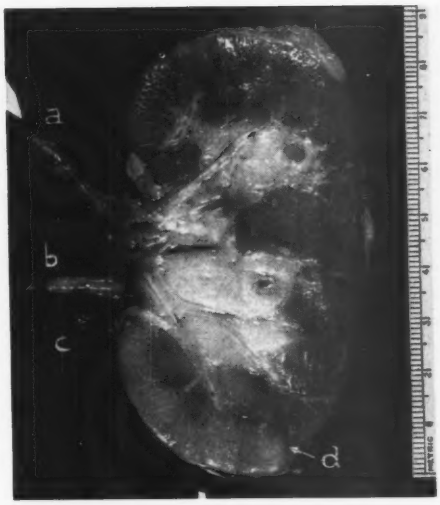


FIG. 4. Case 2. The ischemic kidney. Note the demarcation (d) between the ischemic portion and the area supplied by the aberrant renal artery (c). The area of thrombosis (a) is visible in the renal artery. The ureter (b) is normal.

Case 3. F. R., a 51 year old white policeman, suddenly developed an attack of dizziness and epigastric pain while walking his beat. The attack was followed by a throbbing headache and blurring of vision. The blood pressure was found to be 250/150, and he was given hypotensive drugs.

Past history revealed that a slight elevation of blood pressure had existed for about six years; the actual values were not known. There was no family history of hypertension.

In March 1953, two months later, he was admitted to the hospital with a blood pressure of 200/130. The fundi revealed grade III eye-ground changes with constriction and sclerosis of retinal arteries, hemorrhages and exudates. Except for enlargement of the heart, the remainder of the physical examination was negative.

Blood urea was 42 mg. per 100 ml.; urea clearance was 70 per cent of normal in the first hour and 64 per cent in the second hour. The urine showed a trace of albumin and occasional white blood cells.

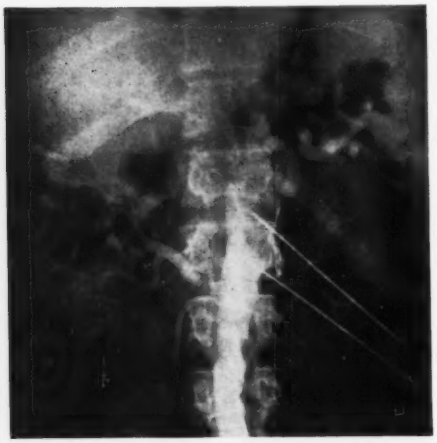


FIG. 5. (Case 3) Visible between the aortogram needles are two small arteries extending to a small, poorly vascularized left kidney. Right renal artery is normal.

The urine culture produced *Escherichia coli* on one occasion; a second culture was sterile. The Addis test showed a specific gravity of 1.017 with 0.36 Gm. of protein excreted in 24 hours; the sediment contained 84,000 casts, 126,000 red and no white blood cells in 12 hours.

Chest roentgenograms revealed left ventricular enlargement. A plain roentgenogram of the abdomen was normal except for a small left renal outline. Intravenous urography demonstrated prompt excretion from the right kidney but there was no evidence of function of the left kidney. A retrograde pyelogram made two months earlier at another hospital had shown a contracted left kidney. Translumbar aortography revealed a large right renal artery and kidney. Supplying the contracted left kidney were two very small arteries (fig. 5).

Blood pressure determinations over a three-week period averaged 193/120 supine and 179/125 upright.

A left nephrectomy with a left thoracolumbar sympathectomy was advised on the premise that, if the disease failed to respond to nephrectomy, only one stage of the recommended sympathectomy would still have to be done. On April 24, 1953, a left nephrectomy was followed by ablation of the left sympathetic chain from the tenth thoracic to the second lumbar ganglia; the splanchnic nerves were removed from high in the chest and from the celiac ganglion.

Three weeks later the blood pressure was 160/107 and the patient was discharged from the hospital. Urea clearance at that time was 90 per cent of normal in the first hour and 65 per cent in the second hour.

One year later, he was readmitted for evaluation, although he was asymptomatic. The blood pressure was 144/90, the blood urea was 31 mg. per 100 ml., urea clearance was 105 and 85 per cent of normal, and the fundi showed grade I constriction and sclerosis but no hemorrhages or exudates. The amount of protein in the urine was within normal range. Eighteen months after operation, the blood pressure was 130/85.

Pathology. The left kidney was small and weighed 120 Gm. The capsule stripped with some difficulty, revealing a greyish-tan granular surface of uniform texture. The cortex measured 0.5 cm. in thickness. The calyces and ureter appeared normal.

The microscopic study was done by Dr. J. B. Hazard. Marked tubular atrophy was present, particularly in the outer half to two thirds of the cortex. A reduction in number of the tubules was evident, and the remaining tubules appeared small and separated by a relatively increased hyaline and fibrous stroma. In the inner portion of the cortex, the tubules appeared intact. The glomeruli were small but appeared well preserved and their capillaries contained some blood but were not distended. An occasional sclerosed glomerulus and some clusters of hyaline glomeruli were seen. The capsular spaces were prominent and filled with granular coagula. No colloid-filled tubules were found. Major intrarenal arteries were not remarkable except for slight hypertrophy of their walls. Arterioles were patent and showed only a moderate amount of fibrous thickening of their intima.

The pathologic diagnosis was renal tubular atrophy and interstitial inflammation compatible with chronic ischemia associated with renal artery obstruction. No intrarenal vascular lesions were evident in the specimen.

Comment: This patient was found to have severe hypertension following an attack of epigastric pain. There were grade III eyeground changes, depression of renal function, and cardiac enlargement. Intravenous urography showed no evidence of left renal function. Translumbar aortography revealed a striking contrast in the blood supply and size of the two kidneys: the right renal artery and kidney were normal, but there was no main left renal artery; instead, there were two little arteries coming directly from the aorta to the upper and lower parts of a small left kidney. While it was considered that this abnormal kidney could be the cause of the hypertension, left nephrectomy was combined with left dorsolumbar sympathectomy to save the patient an additional operation if nephrectomy did not

lower the blood pressure. (These circumstances are similar to those in two cases reported by Thompson and Smithwick.[3]) The left kidney was contracted and showed changes characteristic of ischemia consisting of tubular atrophy and increased interstitial fibrosis without much change of the glomeruli, intrarenal arteries or arterioles. Following nephrectomy, his blood pressure gradually reached normotensive levels. He has remained asymptomatic and normotensive for almost two years. Since it is well known that unilateral dorsolumbar sympathectomy will not alter the course of hypertensive vascular disease, it is reasonable to assume that the ischemic kidney was the cause of this man's hypertension.

Case 4. This case has been reported by Fisher and Corcoran[2] and will be presented in summary only.

A 14 year old white boy was seen in June 1951 because of hypertension and attacks of abdominal pain. There was no family history of hypertension. The blood pressure was 238/160 in the left arm and 256/100 in the left leg. Tests of renal function gave normal results and the urinary sediment was normal. Neurogenic, endocrine, cardiovascular and intrarenal causes of hypertension were believed to be excluded. He gave a history of intermittent pain in the flanks and abdomen.

The intravenous urogram showed prompt, satisfactory excretion from both kidneys, although the right kidney was somewhat reduced in size. A translumbar aortogram was originally interpreted as showing normal renal arteries and vascularity but, reviewed in the light of later experience, showed poor filling of both renal arteries and their branches. At operation, the right kidney was smaller than the left, and no pulse was felt in the right renal artery. The right kidney was removed and since blood did not flow from the aortic stump of the renal artery, a probe was passed; it met resistance, apparently at the orifice of the renal artery. The boy died four days later. Autopsy revealed congenital coarctation of the abdominal aorta of the segment involving the origin of superior mesenteric artery and renal arteries. There was severe stenosis of the orifices of the renal arteries, superior mesenteric artery, and the celiac axis, due to arteriosclerosis of the fibrous intimal type. The kidneys, which had been protected from the impact of elevated blood pressure by the arterial stenosis, microscopically showed normal tubules, glomeruli and arterioles.

Comment: The fourth case report is summarized as an example of fatal renal hypertension resulting from stenosis of the aortic orifices of both main renal arteries. This was associated with coarctation of the abdominal aorta; the stenotic lesions were attributed to abnormal "jet" effects. Evidently the stenosis of the renal arteries allowed some blood to flow through, but in an impeded manner and with resultant renal ischemia, particularly of the right kidney as shown at operation. In spite of this, the intravenous urogram demonstrated prompt and satisfactory function of both kidneys. Pathologic examination showed no evidence of vascular disease or atrophy within the kidneys. Had the lesion been recognized, one autogenous renal graft might have been lifesaving.

Discussion

Retrospect. That hypertension can be associated with unilateral renal disease was first pointed out by Ask-Upmark[4] in 1929. Further attention was called to this relationship in 1937 by Butler[5] who was the first to report the beneficial effect of nephrectomy upon hypertension in unilateral pyelonephritis. Meanwhile, experimental production of renal hypertension in dogs[1] and other animals,[6, 7] by constriction of renal arteries, stimulated great interest in hypertensive patients with seemingly unilateral renal disease. Nephrectomy frequently was done in the hopes of removing the cause of the hypertension. Results often were disappointing. Actually, removal of abnormal kidneys in hypertensive patients favorably altered the course of the disease in only one out of four or five for a year or longer.[8, 9] This experience indicated that unilateral renal disease was not commonly a primary cause of hypertension, at least, at the time of nephrectomy. The best results of nephrectomy were obtained in patients who had rapidly progressive hypertension of recent onset and in whom there was satisfactory demonstration of disease in only one kidney. Common among the urologic diseases for which nephrectomy was done in the hope of reducing blood pressure were pyelonephritis, pyonephrosis, calculous disease, tuberculosis, aplasia and hydronephrosis.

Gradually, over the last two decades, an increasing number of reports have appeared describing unilateral renal artery occlusion as a

cause of persistent hypertension. Some of these cases have been successfully treated by surgery. This situation, in contrast with many other renal diseases, closely resembles experimental renal hypertension elicited by partial compression of a renal artery.

Etiology: Yuile[10] reviewed occlusive lesions of the main renal arteries in hypertensive patients and classified their etiologies as either extrinsic or intrinsic. Extrinsic causes of renal artery occlusion are aortic or renal artery aneurysms, hematomas, compression by adjacent cyst or tumor and twisting of the renal pedicle. Intrinsic causes of narrowing or occlusion of the renal artery are arteriosclerotic plaques, syphilitic arteritis, thrombosis, embolism and congenital or arteriosclerotic stenosis of the aortic orifice of the renal artery.

Arteriosclerotic narrowing of renal arteries is a common finding at autopsy and usually is associated with widespread arteriosclerosis. Several investigators[11, 12] attempted to show a correlation between arteriosclerotic constrictions of the renal artery and hypertension, but others[13, 14] were unable to demonstrate any relationship between the caliber of the renal artery and the level of blood pressure. Yuile[10] pointed out that arteriosclerotic lesions of main renal arteries usually were associated with intrarenal arteriosclerosis and that pre-existing hypertension probably was a cause of both these lesions, rather than a result of the one.

Several cases have been reported of rapidly fatal, malignant hypertension caused by embolic occlusion of the renal artery in which the autopsy findings were carefully correlated with the clinical data.[15, 16, 17] Transient hypertension has been reported to result from renal vascular injury due to embolus.[15, 18, 19] The longest reported duration of hypertension following renal infarction of this type is 21 days. The size of the embolus and the extent of the renal infarction determine the course following such a vascular injury.

It should be pointed out that renal infarction can occur without causing hypertension. Regan and Crabtree[20] reviewed the literature and summarized the important clinical and pathologic data of 94 patients who had arterial, venous, or traumatic infarction of the kidney. Hypertensive vascular disease was not reported to be present in this group of patients. Most were considered to have complete aseptic infarction of the kidney, and many were subjected to surgery shortly after the onset of symptoms. In others, the diagnosis was presumptive, the patients recovering without surgery.

Infarction of the kidney usually results in complete loss of excretory function and destruction of the kidney. Partial infarction, however, produces areas of atrophy in the renal cortex surrounded by normal tissue. Decrease in renal size results, but excretory function may seem to remain unchanged unless accurately measured and compared with the opposite kidney. Cases of patients with hypertension resulting from such a renal injury have been reported.[21, 22]

Of particular clinical interest are the unilateral thrombotic renal artery lesions which cause sudden onset of renal hypertension. A number of case reports have been published which present the clinical history and pathologic findings at autopsy. Reports have appeared of 16 patients successfully treated by nephrectomy or thromboendarterectomy, with restoration of normal blood pressure. These are summarized in table 1.

Renal Pathology: A review of the vascular and renal lesions, found in three patients with unilateral renal artery occlusion and with the syndrome of malignant hypertension, was presented by Laforet.[23] In two instances the renal artery was occluded by a thrombus; the renal artery of the third patient was obstructed by a metallic foreign body. Microscopic examination of the ischemic kidneys supplied by the occluded arteries showed tubular atrophy, increase in interstitial tissue, and a benign type of nephrosclerosis. The nonischemic kidneys, which were supplied by patent renal arteries, all showed necrotizing arteriolar lesions, characteristic of malignant nephrosclerosis. This accords with the view that renal artery obstruction protects arterioles of the ischemic kidney; whereas, under the impact of hypertension, the kidney with the normal renal artery develops malignant nephrosclerosis.

In animals, the severity of experimental renal hypertension depends in part upon the proportion between ischemic and nonischemic renal tissue. That this may hold true in human

TABLE 1.—*Nonembolic Renal Artery Occlusion with Renal Hypertension*

Autopsy Reports			Relief of Hypertension by Nephrectomy or Thromboendarterectomy		
Author	Year	No. of cases	Author	Year	No. of cases
Freeman and Hartley[28]	1938	1	Leadbetter and Burkland[42]	1938	1*
Stewart[29]	1940	1	Boyd and Lewis[21]	1938	1
Saphir and Ballinger[30]	1940	1	Perry[43]	1945	1
Riggs and Satterthwaite[31]	1941	1	Shea and co-workers[44]	1948	1
Yuile[10]	1944	2	Cornwell[45]	1949	1
Bumpus[32]	1944	1	Malisoff and Macht[46]	1951	1
Goodyear and Beard[33]	1947	1	Owen and Pearlman[47]	1952	1
Schwartz and Gross[34]	1949	1	Thompson and Smithwick[3]	1952	2
Adams and co-workers[35]	1951	2	Howard and co-workers[22]	1954	4†
Aronson and Sampson[36]	1951	1	Bourne[48]	1954	1
Goodman[37]	1952	1	Freeman and co-workers[26]	1954	1‡
Fisher and Corcoran[2]	1952	1	Poutasse (this report)	1955	3
Bauer and Forbes[38]	1952	1	DeBakey[27]	1955	1‡
Blahd and co-workers[39]	1952	1			
Laforet[23]	1953	3			
Ehrlich and co-workers[40]	1953	1			
Hussar and Bornstein[41]	1954	1			
Total		21	Total		19

* Later evidence showed that this was not an occluded renal artery.

† Two additional cases are included in this report: one case was first reported by Boyd and Lewis[21]; the other was found to have a ganglioneuroma pressing on the renal artery with no intraluminal arterial disease.

‡ Thromboendarterectomy.

beings is illustrated by the course of the first patient, who had a small area of ischemic atrophy in one kidney. Five months after the presumed arterial occlusion, his blood pressure was 240/130; a month later the fundi revealed moderate angiospasm but renal function was unimpaired. In contrast, the second and third patients developed hypertension within three months of the time when renal artery occlusion probably occurred. Both manifested severe hypertensive vascular disease as shown by eye-ground changes and depression of renal function. The extent of renal ischemia and atrophy in the second patient was subtotal, while the third patient had involvement of the entire kidney. The fourth patient did not show ischemia pathologically but had incomplete occlusion of both renal arteries and good evidence of intermittent grossly deficient renal blood supply.

DIAGNOSIS

It is important to bear in mind the possibility of renal hypertension in a patient who has sudden onset of nonfamilial hypertension. Of particular interest are those patients who have abdominal pain or disease and soon after develop progressive hypertensive vascular disease. The abdominal symptoms may be brief or prolonged and investigation often fails to reveal the source of disease. The symptoms may not resemble the usual type of pain associated with renal disease. Intravenous urography usually will show absence or severe diminution of renal function in the ischemic kidney with complete renal artery occlusion. If only part of the arterial system is occluded, the kidney may show slight diminution of function or even appear normal.

Retrograde catheterization of ureters should be done and specimens collected from each kidney. The ischemic kidney will show reduction in function consisting of diminished urinary flow, delayed indigo-carmine excretion and decreases of mannitol and para-aminohippurate outputs and urea and creatinine concentrations. Retrograde pyelograms may show a normal pelviocalyceal system or there

may be some reduction of the size of the system with decrease of renal mass.

Translumbar aortography is *the one definitive method* by which occlusive renal artery disease can be demonstrated. It should be utilized in patients suspected of having this type of lesion as the cause of hypertension. It may demonstrate absence of filling of a main renal artery, filling defects in the renal artery, absence of important branches of the main renal artery and reduction in the vascular system of the affected kidney. After complete main renal artery occlusion, blood may be seen to enter the kidney only through aberrant arteries.

With proper safeguards translumbar aortography is safe and is relatively simple.[24] The technic has been previously described[25] and the procedure usually is done under local anesthesia. The technic consists of the insertion of a long needle into the aorta at the level of the first lumbar vertebra in the vicinity of the renal arteries. A preliminary injection of 10 ml. of 30 per cent contrast medium is made to be sure that the needle is inserted correctly. After inspection of this film, 10 ml. of 70 per cent medium is injected for the final film. The iliac arteries are occluded by a pressure pad to prevent down-flow during the injection. Excellent films are obtainable when the procedure is done under local anesthesia since the patient can cooperate by holding his breath during the injection and film exposure. A brief sensation of warmth is felt in the lower abdomen and legs. Approximately 250 translumbar aortograms have been done here by this method without serious complications. We have used Urokon,* but we are now utilizing 50 per cent Hypaque† as a contrast medium.

Treatment

The treatment of hypertension associated with ischemic atrophy of the kidney, resulting from unilateral renal artery occlusion, is nephrectomy (table 1). Function of the kidney with intact blood supply must, of course, be reasonably good. Relief of hypertension has consistently followed nephrectomy for this disease, including the first three cases reported here. Once the condition is recognized, nephrectomy should not be delayed. Considerable evidence[23] indicates that the type of hypertensive vascular disease associated with unilateral renal artery occlusion is rapidly progressive, as in the second and third patients (cases 2 and 3). If untreated, malignant nephrosclerosis will occur in the nonischemic kidney and death will result from renal insufficiency.

There has been one report of a patient with partial occlusion of the left renal artery and thrombosis of the aorta, who was relieved of hypertension by thromboendarterectomy of the aorta and renal artery.[26] Preoperatively, the affected kidney was said to have had normal excretory function; unfortunately it was not biopsied, but it is unlikely that atrophy had occurred. In a personal communication, DeBakey[27] reports a similar instance of a patient relieved of hypertension by thromboendarterectomy. Perhaps more patients will be found who have hypertension resulting from partial occlusion of a renal artery, with no loss of function or atrophy, who can be successfully treated by thromboendarterectomy.‡

Summary

Reports of three cases of unilateral renal artery occlusion associated with renal hypertension are presented. In all three patients, the hypertensive vascular disease was relieved following nephrectomy. The affected kidneys revealed ischemic atrophy, particularly of the tubules; the extent of atrophy depended on the amount of normal blood supply that remained intact. These three cases closely simulate experimental hypertension induced by a renal arterial clamp. A summary is also presented of the case of a patient who had stenosis of the aortic orifice of both renal arteries associated with renal hypertension.

Important points in the diagnosis of this lesion are: abdominal or flank pain followed by sudden onset of hypertension in a patient with

* Urokon sodium, Mallinckrodt Chemical Works.

† Hypaque sodium, Winthrop-Stearns, Inc.

‡ Since preparation of this article, two additional patients, having occlusion of a renal artery associated with malignant hypertension, have been treated by nephrectomy. The findings in these cases will be reported in a subsequent publication.

o family history of hypertension; demonstration of unilaterally diminished renal function by intravenous urography or by comparison of samples of urine from each kidney; and most importantly, aortographic visualization of partial or complete occlusion of a main renal artery or one of its major branches.

Hypertension, associated with primary occlusion of a renal artery and renal atrophy, is treated by nephrectomy; thromboendarterectomy may be the treatment of choice in cases in which recent thrombosis of a renal artery has resulted from propagation of a primary aortic thrombosis.

Summario in Interlingua

Es presentate tres casos de occlusion unilateral del arteria renal associate con hypertension renal. In omne le tres casos le morbo vascular hypertensive esseva alleviate post le nephrectomia. Le renes afficite revelava atrophia ischemic, specialmente del tubulos. Le grado del atrophia dependeva del portion intacte del apporto normal de sanguine. Iste tres casos simulava multo directemente le typo de hypertension que es inducite experimentalmente per le application de un clamp al arteria renal. Es etiam presentate summarimente le caso de un patiente qui habeva stenosis del orificio aortic de ambe arterias renal associate con hypertension renal.

Importante aspectos in le diagnose de iste lesion es: (1) Dolor del abdomine o del flanco sequite per le subitanee declaration de hypertension in un patiente sin historia familial de hypertension. (2) Demonstration de diminution unilateral del function renal, effectuate per urographia intravenose o per un comparation de specimens de urina ab cata un del renes. E (3)—lo que es le plus importante—visualisation aortographic de occlusion partial o complete de un arteria renal principal o de un de su principal brancas.

Hypertension associate con occlusion primari de un arteria renal e atrophia renal es tractate per nephrectomia. Thromboendarterectomia pote esser le tractamento seligite in casos in que thrombosis recente de un arteria renal ha resultate ab le propagation de un primari thrombosis aortic.

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A Study of Heart Sounds and Murmurs by Direct Heart Recordings

By CHARLES A. BERTRAND, M.D., IAN G. MILNE, M.D. AND RICHARD HORNICK, M.D.

A method is described for recording heart sounds and murmurs on the surface of the heart chambers and great vessels. Studies were performed on normal dogs and in those with murmurs of known origin, chiefly pulmonic and aortic stenosis. In addition, the reappearance of the murmurs in such cases was studied, following the release of caval occlusion. It was found that the systolic murmur of pulmonic stenosis returned almost immediately after release of caval occlusion, whereas the aortic murmurs did not return until usually from six to 10 beats after release. This may provide a basis for the differentiation of right heart and left heart murmurs by a carefully controlled Valsalva maneuver.

DESPITE technical advances in phonocardiography, the source of many heart murmurs remains obscure. One example is the basal systolic murmur in patients with atrial septal defects. To investigate further the origin of heart murmurs, an experimental technic has been developed in which sounds are recorded directly from the heart and great vessels in dogs. This technic has been used to record heart sounds in normal control animals, and immediately after the production of a defect in the atrial septum. In addition, in order to test the hypothesis that recording directly from the heart's surface would identify the site of origin of murmurs, experiments were carried out in which aortic or pulmonic stenosis was produced. In the course of these experiments, it was also possible to evaluate the test suggested by Zinsser and Kay[1] in which "right heart" and "left heart" murmurs may be differentiated by the length of time required for the murmur to return, following a Valsalva maneuver.

METHODS

The recording of sounds from the surface of the heart chambers was described by Wiggers and Dean in 1917,[2] using a Frank capsule. This method, and similar technics reported subsequently by others,[3, 4] involve suturing of part of the recording apparatus to the heart wall. Since the use of sutures makes it difficult to record rapidly and consecutively from a number of different sites and is not practical on the great vessels, suction was used in our experiments to secure the pick-up device.

A round brass cup measuring 1.9 cm. in diameter is used to transmit sounds from the heart surface. It consists of an inner funnel-shaped cup which is separated from an enclosing outer cup by a space of 1 mm. (fig. 1). The outer chamber so formed is connected via plastic tubing and a three-way stopcock to a constant suction apparatus. The stopcock allows suction to be interrupted, without varying the degree of suction which is maintained at minus 15 inches of mercury. The large inner chamber is connected via a 7 cm. length of plastic tubing of 0.6 cm. internal diameter to a crystal microphone.* The signal from the microphone is transmitted to an amplifier which has two outputs, one to an oscilloscope for visual monitoring during the experiment, and the other to a mirror galvanometer in a Hathaway recording apparatus.†

In order to determine the frequency response of the complete recording circuit, an alternating current generator was used to drive a condenser microphone. This microphone and the brass cup, which is ordinarily applied to the heart surface, were encased in a suitable housing to assure proper apposition of the surfaces and to decrease extraneous noise. The condenser microphone was then used as a calibrated sound generator. To ensure that the intensity of the sound signal remained constant over the frequency range tested, a carrier frequency circuit was used to measure directly movement of the condenser mem-

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* Cambridge Instrument Company, Inc., Ossining, New York.

† A Hathaway S14C oscillograph using an OC2 bifilar type galvanometer was employed. The galvanometer has an undamped natural frequency of 2,000 cycles per second, a damped peak with a 10 per cent rise at 550 cycles per second, and its response is 100 per cent at 700 cycles per second. The resistance is 7 ohms and the sensitivity 5.4 mm. per milliammeter.

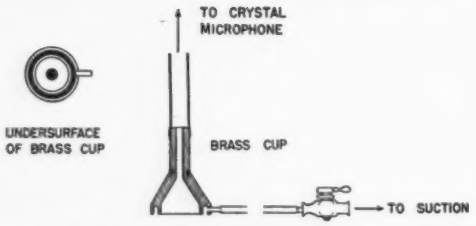

FIG. 1. A drawing of the brass cup used to record sounds from the surface of the heart.

brane. This movement was measured visually on an oscilloscope and necessary adjustments were then made by means of a potentiometer in the alternating current generator circuit. The frequency response of the amplifier alone and the complete recording apparatus is shown in figure 2.

Standard lead II of the electrocardiogram was recorded simultaneously with the heart sounds on a second galvanometer as a timing reference. A third galvanometer was often used to record pressures with a Lilly manometer from the right atrium, right ventricle, pulmonary artery or aorta; or for recording a direct epicardial lead. The paper speed was 8.2 cm. per second; since it was estimated that measurements could be made to within 0.5 mm., the error of measurement of sound duration corresponded to 0.006 second.

Studies were carried out in 32 dogs varying in weight from 8.2 to 19.1 Kg. The first 12 were anesthetized with intraperitoneal pentobarbital sodium; the remainder received morphine sulfate 3 mg. per Kg. subcutaneously, followed in 20 to 40 minutes by a mixture of equal parts of Dial-urethane* and pentobarbital sodium (50 mg. per milliliter) in the range of 0.25 ml. per kg., given intravenously. After the dogs were properly anesthetized, sounds were recorded from the chest wall in the second right intercostal space, the second to fourth or fifth left intercostal spaces, and over the apex. Following this, the trachea was intubated, an intermittent positive pressure respirator connected, and the chest opened. Sounds from the heart and great vessels were recorded in the following locations: (1) Left ventricle —mid-anterior portion, adjacent to the septum. (2) Right ventricle—mid-anterior portion. (3) Left atrium—at the junction of the auricular appendage and atrial wall. (4) Right atrium—at the junction of the auricular appendage and atrial wall. (5) Aorta—2 to 4 cm. distal to the aortic valve (suction often not used here). (6) Pulmonary artery—2 to 3 cm. distal to the pulmonic valve.

In five experiments, the records obtained while using suction were compared with those obtained from the same site while holding the cup manually

* Kindly supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

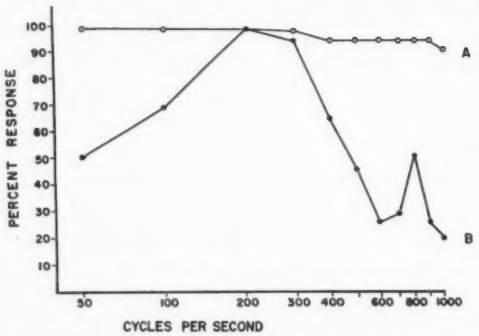

FIG. 2. Frequency responses of the recording apparatus. *A* represents the frequency response of the amplifier; *B* the response of the overall system including the brass cup, crystal microphone, amplifier and galvanometer.

against the epicardial surface. Records obtained by manual apposition of the cup showed no reproducibility of sounds. The records show less extraneous noise and were more reproducible when suction was used. In these experiments, an epicardial electrocardiographic lead was recorded using the brass cup

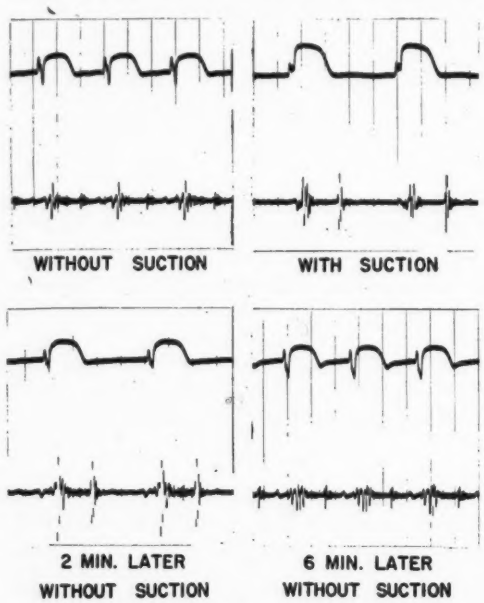

FIG. 3. Current of injury, mid-right ventricle. Simultaneous heart sounds and epicardial electrocardiogram recorded from the same site on the right ventricle. Suction has produced a current of injury and its regression, following release of suction, is illustrated. The records show less extraneous noise when suction is applied.

is a conductor. At all times, slight S-T elevation was present when the brass cup was placed on the epicardium but, during suction, a marked "current of injury" appeared which regressed when suction was discontinued (fig. 3).

Results

Normal Sounds: Nine preliminary experiments were necessary in order to obtain a reasonably proficient technic, to determine the optimum type of pickup and resolve other technical problems. These experiments are not included in the following observations.

Normal control sounds were obtained on the chest, heart, and great vessels in 23 dogs. Figure 4 illustrates the sounds recorded from the chest and figure 5 from the heart and great vessels in one such animal. The duration of the heart sounds at each site was measured and the mean and range of values are shown in table 1.

The relative intensity of first and second sounds on the left side of the heart was quite consistent. In all dogs, the first sound was much louder than the second over the left ventricle and the converse obtained for the aorta. The left atrial first sound always exceeded or equalled its corresponding second sound. On the right side, however, the findings were variable. On both the right ventricle and pulmonary artery the sounds were often equal but, occasionally, either the first or second sound was the louder. On the right atrium the first sound was usually louder than the second. The atrial sounds were of greater intensity than those recorded on the ventricular surface.

The second pulmonic sound varied in duration from 0.039 to 0.065 second in 19 dogs and averaged 0.055 second. In four dogs the second sound from the pulmonary artery was clearly split. In these cases this sound averaged 0.088 second in duration ranging from 0.079 to 0.095 second. Figure 6 illustrates such a split pulmonic second sound with a simultaneous aortic recording showing a systolic murmur. The first component of the split sound corresponds in time to the second aortic sound.

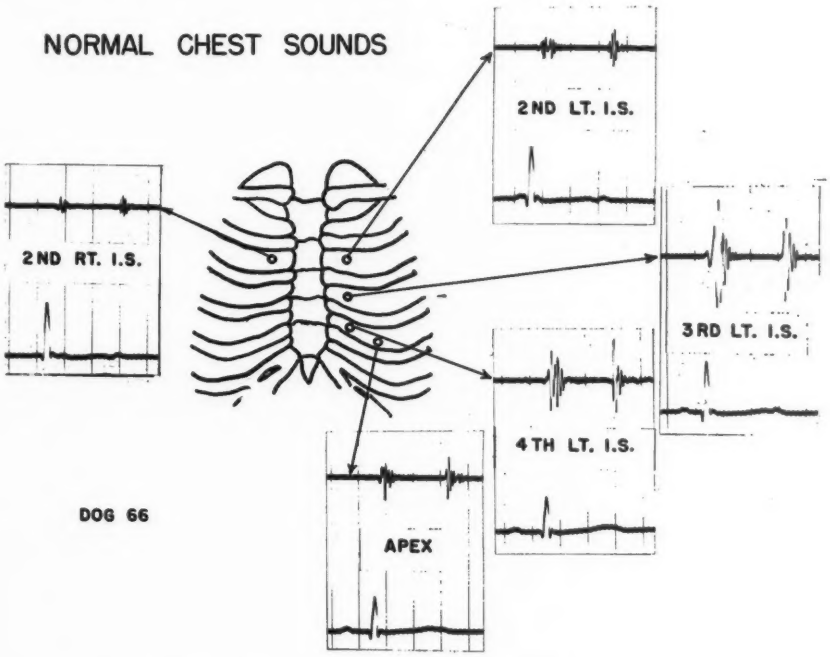

Fig. 4. Normal heart sounds, recorded from the chest in a normal dog

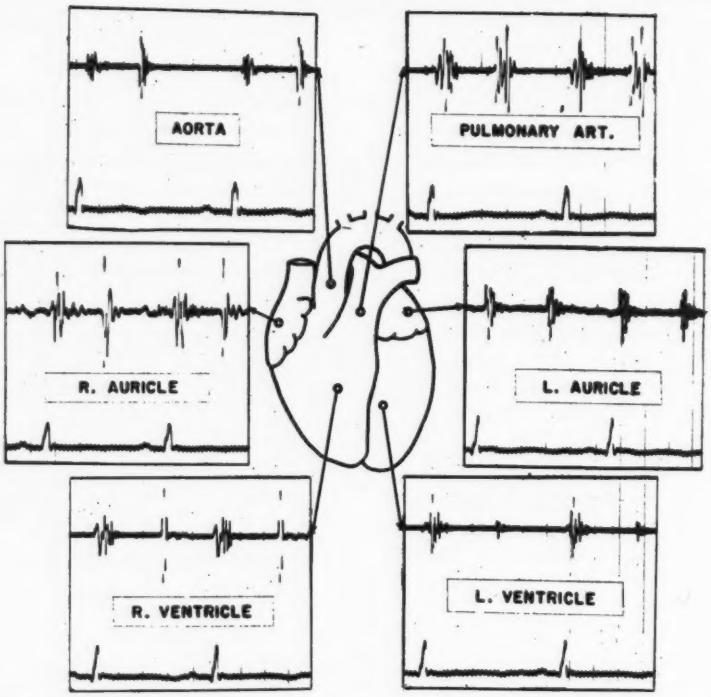

FIG. 5. Heart sounds recorded on the surface of the heart and great vessels in the same dog as in figure 4.

Simultaneous sounds recorded from the surface of the right ventricle and right ventricular pressure tracings are illustrated in figure 7.

Atrial Septal Defect: In eight animals an attempt was made to produce an atrial septal defect by incising the septal wall. In five experiments an attempt to produce such a defect resulted in failure, as determined by later necropsy study. In none of these five experiments was a murmur produced over the four cardiac chambers or great vessels. In three animals atrial defects measuring respectively 0.2 cm., 0.5 cm. and 1.0 cm. in diameter were produced, the last being approximately one-half the area of the septum. Phonocardiograms were made up to 60 minutes after the production of the defect and in none of these animals was a murmur produced in any of the six recorded locations. Figure 8 shows the sounds recorded after the production of a 1 cm. diameter defect.

Production of Murmurs: In order to study the characteristics of a heart murmur of known origin, a ligature was placed about the

TABLE 1.—*Duration of Sounds Recorded on the Heart Chambers and Great Vessels*

	Duration of Heart Sounds in Seconds											
	Aorta		Pulmonary Artery			L. Ventricle		R. Ventricle		L. Atrium		R. Atrium	
	1st	2nd	1st	2nd	Split P_2	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Average	.069	.043	.077	.055	.088	.087	.038	.084	.043	.083	.040	.090	.044
Range	.055 .085	.035 .055	.063 .095	.039 .065	.079 .095	.061 .103	.031 .049	.073 .098	.032 .061	.067 .096	.031 .049	.077 .104	.034 .056

ain pulmonary artery or aorta. By occluding hese vessels to approximately one-half their ormal diameter, a loud systolic thrill and murmur was consistently produced. The murmur was well propagated distally, along he vessel, but not proximally. The murmur vas not transmitted to the other cardiac hambers or to the opposite great vessel.

Ligatures were placed about the aorta and ounds recorded from the four cardiac chambers and both great vessels in eight dogs. In each case a loud aortic systolic murmur was recorded and the murmur was not present in any of the other areas in seven of the eight animals. One dog had lower frequency vibrations over the main pulmonary artery as well; these occupied the first one-third to one-half of the systole and were of low intensity. Whether this represents transmission of the aortic murmur or is due to the operator's holding the pickup too tightly against the thin-walled pulmonary artery (and thus producing some degree of stenosis) remains conjectural.

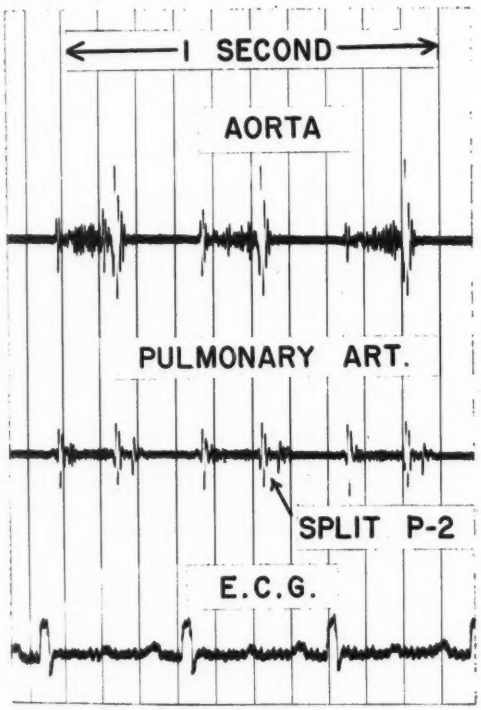

FIG. 6. Illustrates simultaneous recordings of sounds obtained from the aorta and pulmonary artery. An aortic systolic murmur and a split pulmonic second sound are noted.

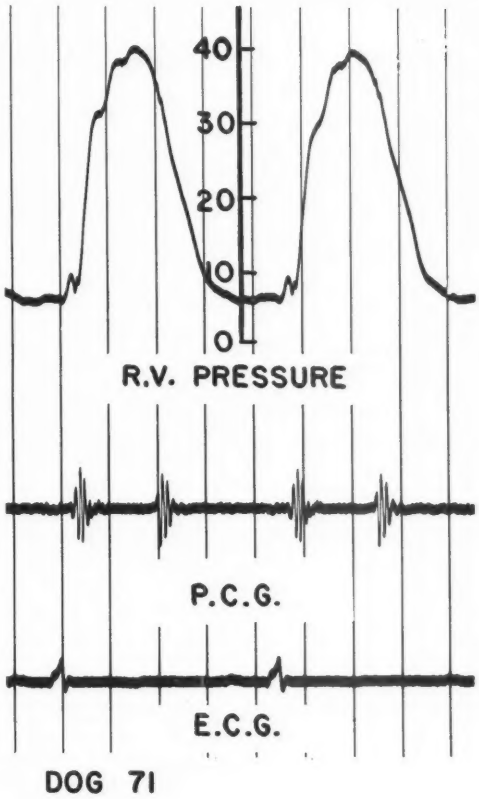

FIG. 7. Simultaneous sounds and pressure recordings from the right ventricle.

In six experiments, a ligature was placed about the main pulmonary artery; sounds were recorded from it, the aorta and the four cardiac chambers. In five of the six dogs there was no transmission of the systolic murmur from the pulmonary artery. In one of the six, there were some low intensity early systolic vibrations over the aorta.

The Effect of Decreased Venous Return on Aortic and Pulmonic Systolic Murmur: In these experiments ligatures were placed around the superior and inferior venae cavae so that venous inflow could be interrupted temporarily

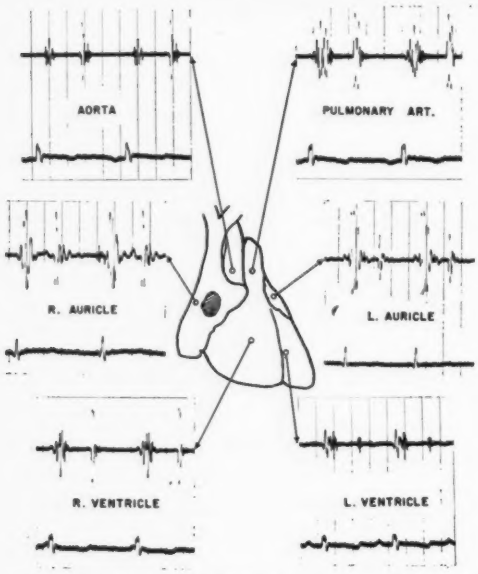

FIG. 8. Atrial septal defect. Sounds on the heart and great vessels, following production of a 1 cm. diameter atrial septal defect. No murmur is present at any recorded location.

when desired, in order to imitate a strong Valsalva maneuver. The azygos vein was ligated in order that the venous return to the right atrium would be limited to coronary sinus flow when both cavae were occluded. Aortic or pulmonic stenosis was produced as above and the resulting murmurs recorded before, during and after five to 20 seconds of venae caval occlusion. One hundred thirteen caval occlusions in 11 dogs were done; 55 in dogs with induced aortic stenosis and 58 in animals with pulmonic stenosis.

In general, the pulmonic systolic murmurs returned to maximal intensity by the second or third postrelease beat, whereas the aortic murmurs returned more gradually, reaching maximal intensity from the sixth to the tenth postrelease beat, as in the experiment shown in figure 10. Figure 11 shows the time elapsed before return of the aortic and pulmonic systolic murmurs, following release of caval occlusion. Within the limits tested, the duration of caval occlusion appeared not to influ-

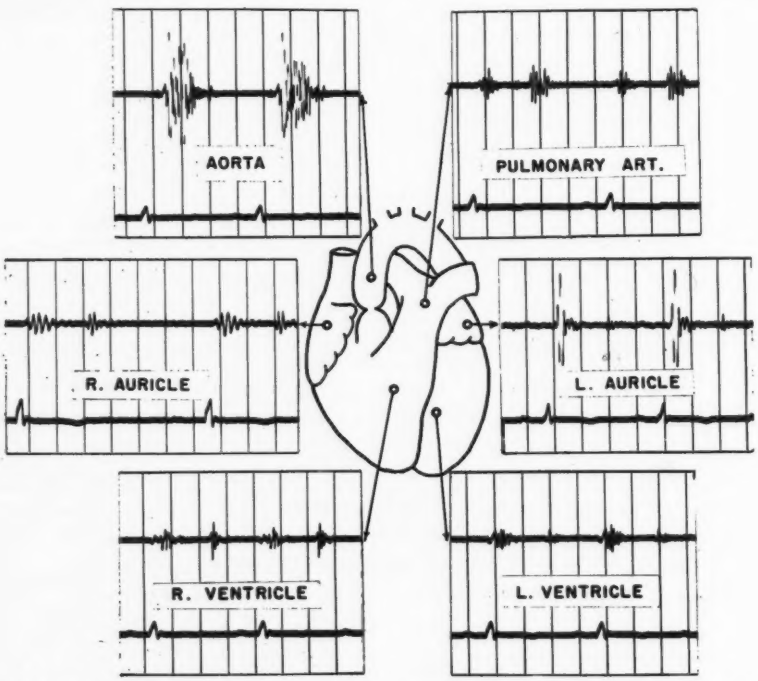

FIG. 9. Caval occlusions. An aortic systolic murmur is shown that is not transmitted to the cardiac chambers or to the pulmonary artery.

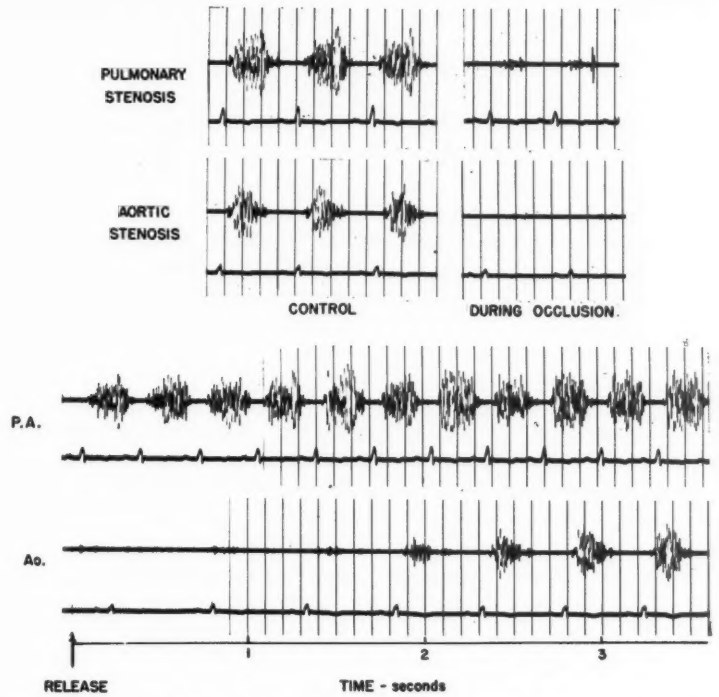

FIG. 10. The contrasting behavior of aortic and pulmonic systolic murmurs in the same dog is illustrated, recorded before, during and after release of caval occlusion. The pulmonic systolic murmur reappears abruptly with the first postrelease beat, whereas the aortic systolic murmur appears more gradually and reaches maximal intensity with the seventh postrelease beat.

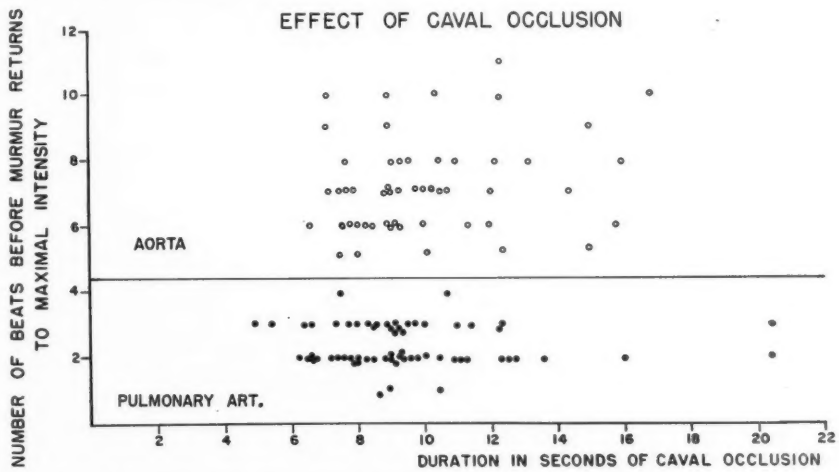

FIG. 11. The duration of caval occlusion plotted against the number of beats required for the systolic murmur to reach maximal intensity, following release of occlusion. Note that the pulmonary systolic murmurs usually reach maximal intensity with the second or third postrelease beat, while the aortic systolic murmurs are delayed in reaching maximal intensity until the fifth to tenth postrelease beat.

ence the interval required for the murmur to return to maximal intensity.

Discussion

The sounds recorded from the various cardiac chambers were, in general, not unexpected. The finding that the first and second heart sounds are of greater intensity on the surface of the atria than elsewhere may be related to the thinness of the atrial wall and the proximity of the pick-up device to the heart valves.

The recording of a split pulmonic second sound localized to the pulmonary artery in 4 of 23 control animals was quite unexpected. The source of the first component of the split sound may arise either in the pulmonary artery from closure of the semilunar valves, or may possibly be transmitted from the aorta. Since the second component is present only on the pulmonary artery, it is probable that this component arises within the pulmonary artery but its source remains unexplained. Leatham,[5] by virtue of simultaneous chest recordings over the pulmonic and aortic areas in man, believes that the first component of a split pulmonic second sound represents aortic valve closure with the second component being due to pulmonic valve closure.

The lack of production of a heart murmur, following creation of an atrial septal defect, sheds no light on the source of such murmurs in man. However, these were acute experiments in open chest animals with recordings being made no longer than one hour following creation of the defect. Clinically, we have observed that, despite apparent adequate surgical closure of an atrial defect, the basal systolic murmur may persist for a variable length of time following operation. These findings suggest that this murmur is related more to the presence of increased pulmonary flow with dilatation of the main pulmonary artery and possible relative pulmonary stenosis, rather than the flow through the atrial defect. Long term animal experiments may clarify this point.

The murmurs produced by placing ligatures about the main pulmonary artery or aorta were in the optimum frequency range of our recording apparatus. Such murmurs (and thrills) were found to be well localized to the site of production and transmitted only distally along the course of the involved vessel. No significant transmission to other cardiac chambers was recorded. Should such localization apply to murmurs of other anomalies, this procedure may provide a basis for the determination of anatomic defects. Intracardiac phonocardiography, utilizing a suitable transducer at the tip of the catheter, may provide such information. These studies are in progress.*

The caval occlusion experiments, with induced pulmonic or aortic stenosis, show a distinct difference in the pattern of response in "left heart" and "right heart" murmurs. Following release of caval occlusion, the pulmonic murmurs returned to original intensity in two to three beats, whereas the aortic murmurs required six to 10 beats to do so. It, therefore, seems possible that a carefully controlled clinical procedure, employing the Valsalva maneuver, can aid in differentiating murmurs arising from the right and left heart.

Summary

(1) Heart sounds have been recorded directly from the surface of the heart and great vessels in 23 normal dogs. Subsequent recordings were made in 14 of these animals with artificially produced aortic or pulmonic stenosis.

(2) Four of the 23 control animals had a split second sound which was localized to the pulmonary artery.

(3) The production of an atrial septal defect in three dogs was not associated with the development of a heart murmur.

(4) Murmurs due to induced aortic or pulmonic stenosis were recorded at their site of origin and were found to be transmitted distally along the involved vessel but not transmitted to other cardiac chambers.

(5) One hundred thirteen caval occlusion experiments were performed in 11 dogs with induced aortic or pulmonic stenosis. Following

* With the aid of Gulton Mfg. Corp., Metuchen, N. J.

release of caval occlusion, the pulmonic murmurs returned to original intensity in two to three beats; in contrast, the aortic murmurs increased gradually, reaching original intensity in six to 10 beats.

Acknowledgments

We are grateful for the advice and guidance given by Dr. William R. Milnor during the course of these investigations. In addition, it is a pleasure to acknowledge the technical assistance of Miss Kate Fleenor, Mrs. W. D. Chester, Mr. Kemp Cole, Mr. L. W. Reynolds and Mr. W. Von Wittern.

Summario in Interlingua

(1) Sonos cardiac esseva registrate directemente ab le superficie del corde e de vasos major in 23 canes normal. Subsequentemente registrationes esseva obtenite ab 14 del mesme animales in que stenoses aortic o pulmonic habeva essite producite artificialmente.

(2) Quatro del 23 animales de controlo habeva un bipartite sono secunde que esseva localisate al arteria pulmonar.

(3) Le production de un defecto atrio-septal in tres canes non esseva associate con le disveloppamento de un murmure cardiac.

(4) Murmures que resultava de inducite stenoses aortic o pulmonic esseva registrate al sito de lor origine; il se monstrava que illos esseva transmittite distalmente al longo del vaso involvite sed que illos non esseva transmittite a altere cameras del corde.

(5) In 11 canes con inducite stenoses aortic o pulmonic un total de 113 experimentos occlusional esseva executate. Post relaxation del occlusion caval le murmures pulmonic retornava al intensitate original post 2 a 3 pulsos. Per contrasto con isto, le murmures aortic se augmentava gradualmente e re-attingeva lor intensitate original post 6 a 10 pulsos.

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Diagnosis of Congenital Aortic Septal Defects

Description of Two Cases and Special Emphasis on a New Method which Allows an Accurate Diagnosis by Means of Cardiac Catheterization

By H. A. H. D'HEER, M.D. AND C. L. C. VAN NIEUWENHUIZEN, M.D.

Two cases of aortic septal defect, diagnosed in life by means of cardiac catheterization, are described. An explanation is given of a method, used in these cases, whereby a correct diagnosis could be made before operation. Other methods for diagnosis and differential diagnosis are discussed.

AMONG congenital cardiac anomalies which are now amenable to cardiac surgery, none is more difficult to diagnose than aortic septal defect. All authors emphasize the difficulty of making a correct diagnosis before operation, and most of the cases which have been described were at first diagnosed as patent ductus, ventricular septal defect, truncus arteriosus or other anomalies. Among 34 cases described in the literature, 17 were diagnosed at necropsy and 12 during operation for patent ductus. On only five cases was the correct diagnosis made before operation: by retrograde aortography in three and by catheterization in two cases.

In our two cases, the diagnosis was made with certainty by the interpretation of the various positions of the catheter during cardiac catheterization.

Since the application of surgery for the relief of these anomalies depends upon correct diagnosis, we will, after a short description of our two cases, review the various methods of making a diagnosis and discuss the differential diagnosis.

CASE REPORTS

Case 1. H. D., a 7 year old girl, was admitted to our Cardiologic Department on March 13, 1953 with the diagnosis of possible atypical patent ductus. Cardiac anomality was first recognized when she was 3 months old.

Her complaints were fatigue, exertional dyspnea and palpitation. There was no cyanosis and she did not squat. There were also complaints of coughing and a history of frequent bronchitis. On physical examination, we found a child with a reddish color, but no cyanosis, and no clubbing of the fingers was present. The blood pressure was 105/70 mm. Hg. A harsh systolic murmur was present in the second to the fourth intercostal space along the left sternal border, beneath the manubrium and in the second and third right intercostal spaces. The second pulmonic sound was extremely loud.

The hemoglobin was 78 per cent, and the red blood cell count was 3,820,000. The electrocardiogram showed evidences of left ventricular hypertrophy with strain. On x-ray examination there was no hilar dance, but an enormous enlargment of the pulmonary artery and great pulmonary engorgement was evident. The heart was enlarged to the right and to the left.

Catheterization was performed for the first time on March 17, 1953. At this time it was possible to pass the catheter into the aorta (fig. 1). The pressures were: aorta 100/55 mm. Hg, mean 72; pulmonary artery 100/65, mean 77; right ventricle 90/0, mean 45 mm. Hg. There were no differences between the pressure curves of the aorta and pulmonary artery. The blood samples showed a slight bidirectional shunt between aorta and pulmonary artery.

In considering the pathway taken by the catheter, it was evident that it did not enter the aorta through a patent ductus, because its position was too far median, and it was lying in the ascending aorta, the tip not reaching the site in the arch at which the ductus arteriosus enters the aorta.

There remained, therefore, two possible routes that the catheter may have followed: an aortic septal defect or a high ventricular septal defect. To secure more information we decided to perform a second catheterization, and to take as many blood samples as possible in the pulmonary artery and in the right ventricle. At the second catheteriza-

From the Cardiologic Section of the department for Cardiac Surgery. St. Anthonius Ziekenhuis, Utrecht, Netherlands.

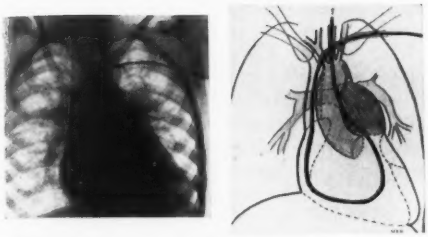

FIG. 1. Case 1. Catheter is in the aorta, having reached it via right ventricle and pulmonary artery.

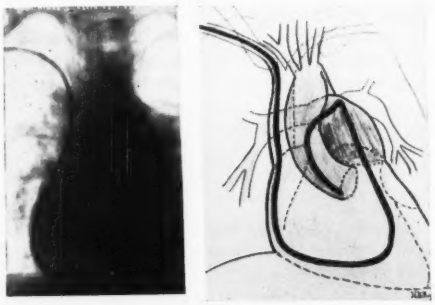

FIG. 2. Case 1. Catheter, via right ventricle and pulmonary artery, passed through an aortic septal defect into the ascending aorta toward the aortic valves.

tion (March 26, 1953), however, it was possible again to guide the catheter into the aorta, but on this occasion downward into the ascending aorta toward the aortic valves rather than upward into the ascending aorta toward the arch (fig. 2). Through these observations, a high ventricular septal defect was excluded, and when the films showing the two catheter positions were superposed, it could be seen that a large defect above the aortic valves must be present (fig. 3).

The child was operated upon on April 24, 1953 by Prof. Dr. A. G. Brom and Dr. A. L. E. Schaepkens van Riempst. A large defect with a diameter of 5 cm. between the large pulmonary artery and the aorta above the semilunar valves was found. The defect was partially closed by a large ligature. The postoperative course was uneventful.

Case 2. C. E., a 6 year old girl, was admitted to the hospital on March 29, 1954. Heart disease was observed immediately after birth by the physician. When she was three months old, she became cyanosed for the first time. At the time of admission, she tired very quickly, had dyspnea and cyanosis and squatted. She had also frequently bronchitis. On physical examination acrocyanosis and slight clubbing were observed. The blood pressure was 110/80 mm. Hg. A systolic murmur varying from

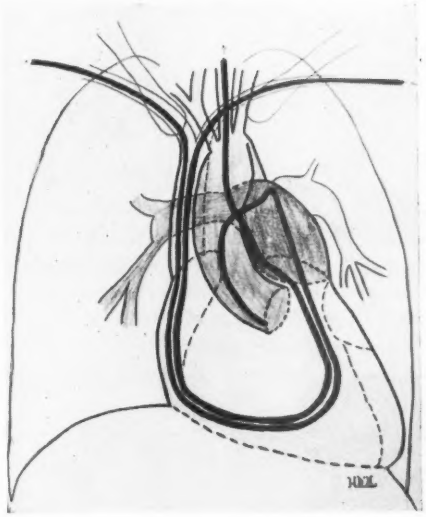

FIG. 3. Case 1. Superposition of the two catheter positions in figures 1 and 2. The defect must be situated in the aortic septum at a certain distance above the aortic valves.

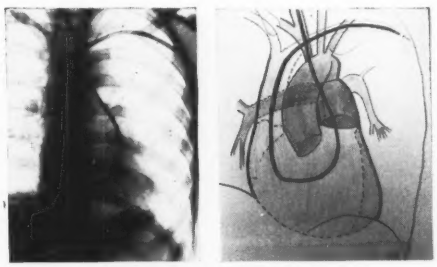

FIG. 4. Case 2. Catheter is in the aorta, having reached this vessel via right ventricle and pulmonary artery.

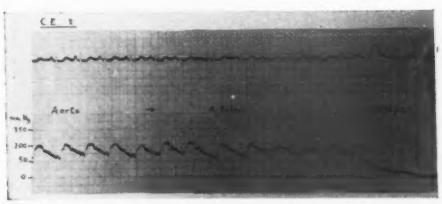

FIG. 5. Case 2. Pressure recording while withdrawing the catheter from aorta into pulmonary artery and pushing it into a "capillary." Note, there is no ventricular pressure pattern between aorta and pulmonary artery pressures, and the two pressures are equal.

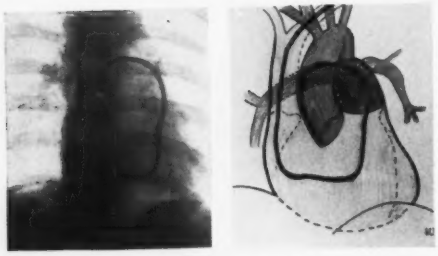

FIG. 6. Case 2. Catheter, via right ventricle and pulmonary artery, passed through an aortic septal defect into the ascending aorta toward the aortic valves.

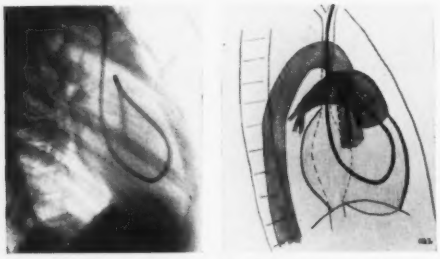

FIG. 7. Case 2. Same catheter position as in figure 6, lateral view.

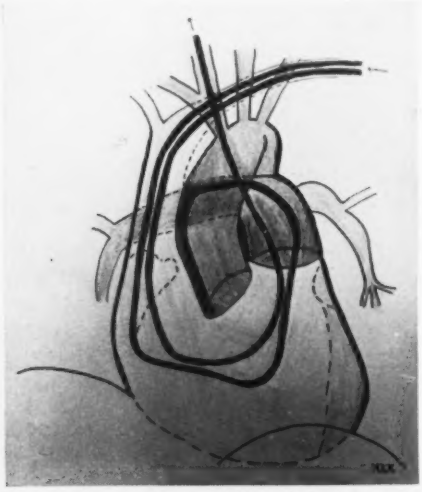

FIG. 8. Case 2. Superposition of the two catheter positions in figures 4 and 6. Here again there must be a defect in the aortic septum at some distance above the aortic valves.

slight to harsh was present over the pulmonary area. The second pulmonic sound was very loud.

Hemoglobin was 110 per cent with 5,406,000 red blood cells. X-ray films showed a somewhat dilated heart, especially the right atrium and the left ventricle. There was pulmonary engorgement, but no hilar dance. The electrocardiogram showed right ventricular hypertrophy.

Heart catheterization was performed on April 4, 1954. The pressure in the pulmonary artery was 110/55, the mean being 85 mm. Hg. Then we were able to put the catheter into the carotid artery (fig. 4). While withdrawing the catheter from the aorta, we could push it into the pulmonary artery "capillary," without obtaining a ventricular pressure recording between aorta and pulmonary artery (fig. 5).

The possibility of an aortic septal defect was then thought of and a second attempt was made to enter the aorta via the defect; and, by manipulating the catheter, to direct it into the ascending aorta toward the aortic valves. This was accomplished (figs. 6 and 7). Again, superposition of the two x-ray films (fig. 8) demonstrated with absolute certainty the presence of an aortic septal defect situated above the aortic valves.

COMMENT

On embryologic grounds, aortic septal defect lies close to truncus arteriosus and the difference is only a matter of gradation. Some authors have designated aortic septal defect as partial truncus. Clinically, aortic septal defect resembles patent ductus and, especially, patent ductus with pulmonary hypertension. It is also frequently mistaken for a high ventricular septal defect.

Diagnosis of Aortic Septal Defect

(*1*) *Clinically*, this condition is a possibility, and we must have this diagnosis in mind, therefore, in any case with a continuous or systolic and diastolic murmur and right ventricular hypertrophy in the electrocardiogram. On x-ray films, there is an enlarged heart and a very large pulmonary artery.

(*2*) *In cardiac catheterization*, the impossibility of catheterizing the aorta when a patent ductus is suspected, always suggests the possibility of an aortic septal defect. When a catheter can be passed into the aorta, the following possibilities exist: *ventricular septal defect* or overriding aorta, patent ductus, truncus arteriosus and transposition of the great vessels.

The difference between ventricular septal defect and aortic septal defect is very difficult

to find out by location of the catheter in the aorta only. However, it may be possible in aortic septal defect, while withdrawing the catheter out of the aorta, to see that the aortic pressure changes into the lower pressure of the pulmonary artery. When, in aortic septal defect, the pressures in aorta and pulmonary artery are equal, it may be possible to withdraw the catheter out of the aorta and push it immediately into the "capillaries" of the pulmonary artery, without obtaining a ventricular pressure pattern between the aorta and pulmonary artery pressures (fig. 5).

Patent ductus is easier to distinguish from aortic septal defect. When the catheter enters the aorta via a patent ductus, it nearly always goes into the descending aorta, without ascending in the arch. In the occasional instance when it starts toward the arch, almost always it will enter the left carotid artery and not the right. Through an aortic septal defect or an overriding aorta, the catheter follows the arch and in that way enters the descending part, or it ascends in any of the carotid or subclavian arteries.

Differentiation of aortic septal defect and *truncus arteriosus* is often very difficult. On determining the oxygen content of various blood samples, both anomalies can give exactly the same picture. Only the method described in this paper, by which catheters are made to take two directions after entering the aorta, can give a complete differentiation.

Transposition of the great vessels gives a totally different clinical picture since it is not possible to place a catheter in the pulmonary artery.

While determination of the oxygen content of blood samples, obtained from the pulmonary artery and right ventricle, may aid in differentiating these anomalies and, particularly, in excluding a ventricular septal defect (or an overriding aorta), the only absolutely sure method of differentiation is to pass the catheter into the aorta via the aortic septal defect and photograph it first, after it has been directed toward the arch and again, after it has been directed toward the aortic valves. X-ray films, thus obtained, will show clearly that the defect is situated in the ascending aorta and at a certain distance above the aortic valves (figs. 3 and 8).

(*3*) *The oxygen content of blood of right brachial artery and femoral artery on effort* can also give much information. This can be used in cases in which a shunt into the pulmonary artery and a pulmonary hypertension are present. On effort the blood of the femoral artery will be more desaturated than that of the brachial artery in the presence of a patent ductus with reversed shunt. However, when there is an aortic septal defect, the desaturation of the blood in the two arteries will be the same, since the shunt will lie proximal to the mouth of the innominate artery. Nearly the same information can be reached by obtaining simultaneous oxymetric readings from both ears, during effort, by means of a two-ear oxymeter.

(*4*) *Retrograde aortography* is also a good method for making a correct diagnosis of aortic septal defect. Since in our cases the diagnosis was confirmed by catheterization, aortography was not necessary, and we have had no experience with this method in the diagnosis of aortic septal defect.

Summary

Two cases of aortic septal defect are described. The correct diagnosis could be made *only* by catheterization of the heart. After the catheter was put into the aorta via the aortic septal defect, it was advanced first in a forward direction toward the aortic arch and carotid artery and then in a backward direction through the ascending aorta toward the aortic valves. By superposition of the x-ray films, showing the two catheter positions, a defect in the ascending aorta, at some distance above the aortic valves, was clearly demonstrated.

Various methods for making a correct diagnosis of aortic septal defect are discussed. It is pointed out that cardiac catheterization yields the most important diagnostic information. This consists mainly in the findings discussed in the preceding paragraph, but also in the oxygen content of blood samples obtained from different chambers and vessels. When great pulmonary hypertension exists, only the method described in the above paragraph insures a correct diagnosis.

Summario in Interlingua

Es describite duo casos de defecto aortico-septal. Le correcte diagnose esseva possibile solmente per catheterisation cardiac. Post que le catheter esseva inserite in le aorta via le defecto aortico-septal, illo esseva movite (1) in avante verso le arco aortic e le arteria carotide e (2) in retro a transverso le aorta ascendente in le direction del valvulas aortic. Per superimponer le pelliculas roentgenographic del duo positiones del catheter, il esseva possibile demonstrar clarmente le presentia de un defecto in le aorta ascendente alique supra le valvulas aortic.

Es discutite varie methodos pro le correcte diagnose de defectos aortico-septal. Nos signala que catheterisation cardiac provide le plus importante information diagnostic. Isto consiste principalmente in le supra-discutite constatationes sed etiam in datos in re le contento de oxygeno in specimens de sanguine obtenite ab varie cameras e vasos. In casos de grande hypertension pulmonar, solmente le supra-describite methodo (vide paragrapho 1) assecura un correcte diagnose.

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The Effect of Intra-arterial Injections of Hydergine and Dihydroergocornine on the Peripheral Circulation in Man

By ROBERT H. GOETZ, M.D.

If given by the intra-arterial route, the immediate effect of the hydrogenated alkaloids of ergot is unpredictable. Vasodilation is obtained in some patients only. However, it was found that in those cases who do not react, the vessels respond more easily to the release of sympathetic tone, proving that, nevertheless, the drug has had an (potential) effect, probably on the neurovascular apparatus. This effect could be demonstrated for many hours and is, therefore, of considerable therapeutic interest. Even with the higher local concentrations possible by the intra-arterial route, the hydrogenated alkaloids of ergot still did not exhibit any adrenolytic action on the peripheral blood vessels in man.

EXTRACT of ergot, widely used for its oxytocic action and notorious for its vasoconstrictor effect, had long been suspected of possessing, in addition, an inhibitory action on the sympathetic nervous system. This sympathicolytic action of ergot has proved of great interest to physiologists and clinicians ever since Rothlin[1] demonstrated its presence in ergotamine. However, such conditions which would have benefitted from the sympathicolytic action, namely, hypertension and peripheral vascular diseases, remained inaccessible, due to the direct vasoconstrictor action still present in ergotamine.[2] The sympathicolytic principle became accessible to the clinician only when Stoll and Hoffman[3] in 1943 succeeded in producing derivatives, which in animal experiments proved void of all vasoconstrictor effects.[4, 5]

Our investigations on the circulatory effect of one of these alkaloids, namely, dihydroergocornine[2, 6] and Hydergine* in man[7] demonstrated that, if given by the parenteral route, they produce bradycardia, a fall in blood pressure and dilatation of the peripheral blood vessels, which suggested some usefulness in the treatment of hypertension. These effects were shown to be partly central in origin and partly dependent on the integrity of the sympathetic nervous system.[2, 6] These findings have subsequently been fully confirmed by numerous investigators.[8-13]

Besides these effects, Goetz and Katz[14] showed that dihydroergocornine may suppress or reverse the blood pressor response to adrenalin, although it was unable to do the same to the vasoconstrictor action of adrenalin on the digital vessels, at least in doses which were sufficient to produce a reversal on the blood pressure.

Whereas hypotension and bradycardia are very constant and can be obtained with the greatest regularity, the vasodilator effect on the peripheral vessels is a capricious effect not invariably produced by intravenous Hydergine. As the blood vessels of the human extremity do not contain vasodilator fibers, ablation of the vasomotor tone alone does not always seem sufficient to produce vasodilatation. As a matter of fact, the failure of sympathicolytic drugs to produce vasodilatation has been quoted in support of the assumption that the blood vessels of the human skin are not supplied by active vasodilators.[23]

Lecture delivered at the South African Medical Congress at Port Elizabeth, October 1954.

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* Hydergine is a mixture of equal quantities of the three hydrogenated ergot alkaloids: dihydroergocornine, dihydroergocristine and dihydroergokryptine and has, in principle, the same action as dihydroergocornine.

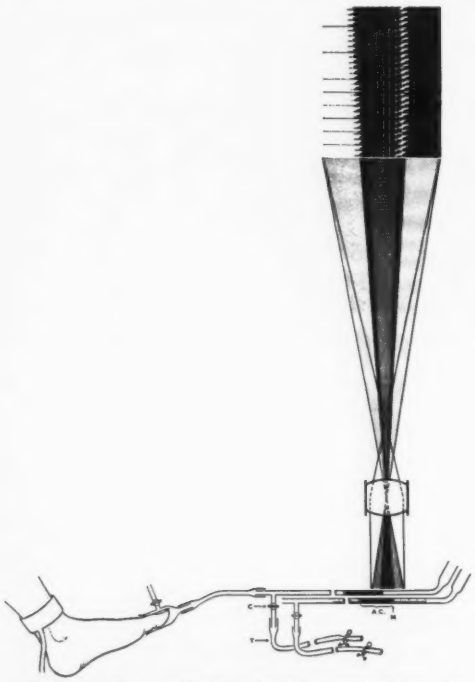

FIG. 1. The optical principle underlying the plethysmographic method employed for recording cutaneous blood flow. That part of the pipette which is filled with alcohol (*A.C.*) acts like a biconvex lens and intensifies the light, giving the appearance of a dark grey or black band on the tracing. The pipette containing air behaves like two plain parallel plates to the light. The light therefore just passes through it giving the grey shade on the film. The meniscus (*M*) reflects the light and casts a shadow on the film—hence the white line between the dark and light shades of grey. The etch marks of the calibration on the pipette absorbs the light and appears as white lines on the film. The system is therefore always calibrated whatever the enlargement. The tap (*C*) and the rubber tubing (*T*) permit adjustment of the meniscus. Two pipettes of equal diameter are mounted next to each other in the same optical system. Thus the blood flow in two limbs can be simultaneously recorded.

Contrary to our experience with intravenous injections of the hydrogenated alkaloids of ergot, Bircher and Cerletti[16] have reported that the intra-arterial injection of Hydergine invariably produced peripheral dilatation in the anesthetized cat. As the validity of experimental data obtained in animals cannot be assumed to pertain to man, particularly with reference to the sympathetic nervous system,[23] the question arose as to whether in man, too, a more constant and reliable peripheral dilator action could be obtained by the intra-arterial route of administration. This question has become of particular interest since, within recent years, intra-arterial (as opposed to intravenous) therapy in cases of peripheral vascular diseases has found many protagonists.[17-19, 25]

Bircher and Cerletti[16] were able to demonstrate that in the anesthetized cat dihydroergocornine readily produced reversal of the adrenalin effect on the peripheral blood vessels, whereas, as already mentioned, our own investigations[14] failed to elicit this effect in man. Our failure, which referred to intravenous injections, challenged an inquiry into the possibility of producing adrenalin reversal by administering the ergot alkaloids by the intra-arterial route, when the drug could reach the peripheral neurovascular apparatus in higher concentrations.

METHOD AND MATERIAL

Continuous records of the peripheral circulation were obtained by means of the optical digital plethysmograph, as described in detail elsewhere.[20] For the present investigation, a portable model, fitted with two pipettes for the simultaneous recording of the blood flow in two extremities, was used.[21] This method is sensitive enough not only to allow the correct registration of the height of the pulse volume, but also the calculation of the arterial inflow at any one moment by means of the so-called venous congestion test. Simultaneously with the blood flow, the respiration and the skin temperature of one or more digits could be recorded with a built-in mirror galvanometer and thermocouples. The heart rate was, of course, available from the plethysmogram. The blood pressure was registered by clinical methods.

All examinations were carried out in a noiseless room with the patient reclining quietly on a couch. The tests were usually carried out after 30 to 60 minutes rest. By that time the volume record showed a minimum of spontaneous fluctuations in the peripheral blood flow.

Reflex dilatation was obtained by immersion of one extremity into a specially constructed tank containing water of 44 to 45 C. An immersion heater connected in series with a thermostat and a stirring propeller were fitted in the tank to keep the water temperature constant at that level.[20, 22] The patient was covered with blankets in order to prevent the dissipation of heat.

In some cases, the drugs were administered slowly by means of an intravenous drip. The rate of the drip was continuously recorded simultaneously with the plethysmogram by means of the photo-electric drop recorder.[15] From the number of drops recorded, the exact amount of drug given could be calculated for any one moment.

For the present investigations 19 patients were subjected to the following procedures:

(1) Intravenous injection of dihydroergocornine or Hydergine.

(2) Intra-arterial injection of dihydroergocornine or Hydergine.

(3) Intra-arterial injection of dihydroergocornine or Hydergine, followed by intra-arterial injection of adrenalin.

(4) Intravenous injection of dihydroergocornine or Hydergine, followed by adrenalin.

(5) Intra-arterial injection of a mixture containing dihydroergocornine and adrenalin.

It will be readily appreciated that by simultaneous recording of the vascular reactions in both limbs, following the intra-arterial injection into one, the effect of the drug on the other limb may be similar to that of an intravenous injection, provided the drug is not destroyed or escapes from the vascular tree during its course through the capillary network.

Ten of the patients were normal from the cardiovascular aspect, varying between the ages of 18 and 49. Two patients suffered from essential hypertension, being 55 and 64 years of age, respectively. One patient, aged 42, had had a stellatectomy. Four patients suffered from acrocyanosis and two from Raynaud's phenomenon. They were selected for these investigations because they regularly exhibited a high vasomotor tone.

In the beginning, 0.3 mg. dihydroergocornine was given, usually into the right femoral artery. Later we used Hydergine, 0.5 to 1.5 cc., throughout.

Results

(1) *The Immediate Effect of Intra-arterial Injection of Dihydroergocornine or Hydergine on the Blood Flow:* The local effect of an intra-arterial injection of Hydergine or dihydroergocornine in doses large enough to produce a general systemic effect, such as bradycardia and hypotension, is unreliable and unpredictable, both in the normal subject and in the patient exhibiting a high vasomotor tone.

The general tendency is to produce either an immediate increase in blood flow up to or above the minimum vasodilatation level, or no reaction in the blood vessels at all. With the doses employed, a moderate improvement in the arterial blood flow of the limb was only seen twice.

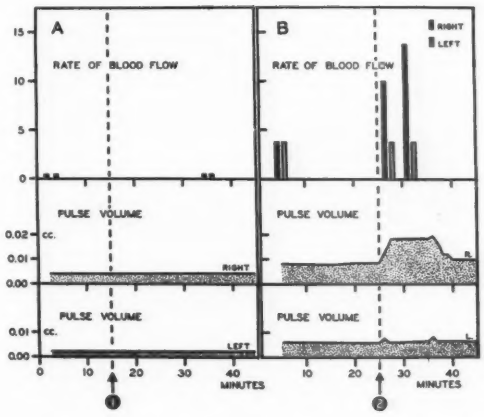

FIG. 2. Injection of 0.5 mg. Hydergine into the right femoral artery in two cases, demonstrating the two extremes in the response obtained. (*A*) Complete lack of response in a case with a high vasomotor tone. (*B*) Immediate dilatation of the vessels, as judged by the increase in pulse volume and rate of arterial inflow, in a case suffering from essential hypertension.

Two extreme reactions are shown in figure 2*A* and *B*. Figure 2*A* was obtained in a young female patient suffering from typical acrocyanosis. As can be seen at a glance, the intra-arterial injection of 0.5 mg. Hydergine into the right femoral artery did not induce any response in the arterial tree of the limb whatsoever. The vessels, being under a high vasomotor tone at the time of the injection, remained constricted, and within 20 minutes there was no change in the height of the pulse volume, digital volume or the rate of arterial inflow. The lack of response is well appreciated from the cuttings of the plethysmogram (fig. 3*A*-*A'*).

Figure 2*B* was obtained from a patient, 55 years of age, who had suffered from essential hypertension for many years. In his case the intra-arterial injection of 0.5 mg. Hydergine into the right femoral artery produced an immediate increase in the arterial circulation, as judged by the rise in pulse volume, digital volume and, particularly, the rate of arterial inflow. The pulse volume, which recorded 0.008 cc. in both toes before the injection, increased in the right within a few seconds and became

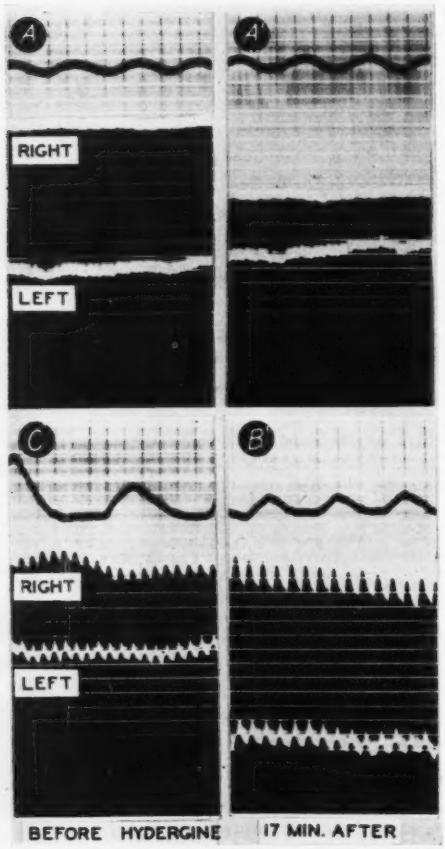

FIG. 3. The effect of an injection of 0.5 mg. Hydergine into the right femoral artery. Cuttings of the plethysmograms obtained in the same two cases as demonstrated in figure 2. (*A-A'*), case 1: Complete absence of response in pulse volume (*C-B'*), case 2: Dilatation obtained in the right leg in the absence of any reaction in the left leg.

established at about 0.015 cc. (fig. 3*B-B'*). The rate of arterial inflow increased from 12 to 42 cc. per minute for 100 cc. of tissue during the same period. The blood flow through the left leg, which was simultaneously recorded, showed no change in this case, although in some patients a temporary decrease could be registered, as judged by the height of the pulse volume and the rate of arterial inflow, provided the intra-arterial injection produced dilatation of the injected limb.

As already indicated above, the intra-arterial injection of Hydergine, although it may not produce any direct peripheral response, eventually brings about the same systemic effect on the circulation as an intravenous injection of the same magnitude. Therefore, provided it is large enough, it will produce a fall in the systemic blood pressure and bradycardia.

Although the intra-arterial injection of Hydergine may produce a powerful vasodilator reaction in the injected limb, it is only occasionally that this is followed by a similar reaction in the remaining limbs.

Similarly, such side-effects as may occur with intravenous injections may also be noted after the same amount given by the arterial route.

(2) *The Effect of Reflex Vasodilatation on the Peripheral Blood Flow following Intra-arterial Injection of Hydergine:* Rothlin[4] drew attention to the fact that the *principle* actions of the ergot alkaloids may be actually *visible*, such as the direct stimulation of smooth muscular organs, or they may be *latent* or *potential*. Into the latter category, he grouped all such effects which are only elicited when the respective organ is activated either by sympathetic stimulation or by circulating adrenalin.

Thinking along these lines, the question arose as to whether the intra-arterial injection of dihydroergocornine, although it may not produce any immediate and "visible" response on the peripheral vessels, did, in fact, produce changes, either on the muscle itself or the neurovascular apparatus, which were "latent or potential" in the sense used by Rothlin and, therefore, could only be demonstrated under certain physiologic conditions involving reflex mechanisms.

In order to answer this question, eight subjects, who did not show any response to the intra-arterial injection of dihydroergocornine or Hydergine, were subsequently submitted to reflex body heating as routinely used for diagnostic purposes in cases of peripheral vascular disease. One arm was immersed in water of 45 C. to a point 6 inches above the elbow for 30 minutes. The dissipation of heat was prevented by means of blankets. In the normal individual this causes reflex dilatation in the remaining extremities. Normally, the response is elicited after a delay of eight to 10 minutes, which is explained by the fact that dilatation

is produced by the increase in the blood temperature resulting from the return of heated blood from the immersed extremity.[22] This causes ablation of the central sympathetic tone in the hypothalamus. In cases exhibiting a high vasomotor tone, and therefore having an initially diminished blood flow through the limb, such as cases of acrocyanosis and Raynaud's phenomenon, it regularly takes considerably longer to initiate dilatation.

As vasodilatation induced by body heating is produced by central ablation of vasoconstrictor tone, it occurs simultaneously in either both lower or both upper extremities, although it does not necessarily occur simultaneously in both the upper and the lower extremities, as the vasomotor tone is generally known to be higher in the latter.[28]

Figure 4 demonstrates the response to reflex body heating following an intra-arterial injection of Hydergine in a patient in whom it did not produce any immediate visible peripheral hemodynamic effect. It refers to a young woman suffering from acrocyanosis, in whom the vessels are normally under a high vasomotor tone and peripheral blood flow is diminished. The injection of 0.5 mg. Hydergine into the right femoral artery did not have any effect whatsoever on the peripheral blood flow in that leg. Twenty minutes after the intra-arterial injection, the digital blood flow was still negligible in both limbs. The pulse volume was hardly registrable in either limb, and the rate of arterial inflow registered only 2 to 3 cc. for 100 cc. of tissue per minute. At this stage, body heating was started by immersing the right arm into water at 45 C. Considering the response in the left leg first, which may serve as a control, we see that, as is typical of cases with vasospastic disorders, 20 minutes pass before the blood vessels begin to dilate. However, once initiated, vasodilatation proceeds and the pulse volume, which before was hardly registrable, rapidly increases to well above 0.020 cc. By virtue of the vasodilatation an increase of 1.20 cc. in the digital volume is recorded, and the rate of arterial inflow increases from 3 cc. to just about 100 cc. per minute for 100 cc. of tissue. After 35 minutes of body heating, the vessels are fully dilated.

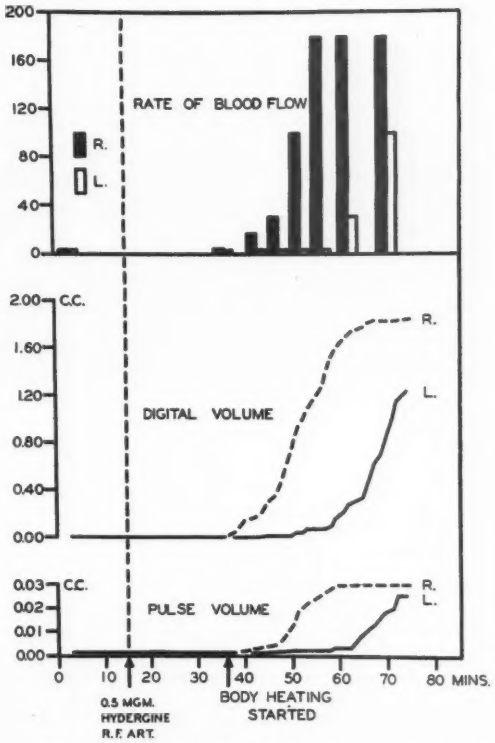

FIG. 4. The effect of body heating on the blood flow in the lower extremities following injection of Hydergine into the right femoral artery. Note, there is no response in the blood flow to the intra-arterial injection itself, but on body heating there is almost immediate and marked dilatation in the right leg, long before there is any response in the left leg. For explanation, see text.

It can be seen in figure 4 that the response of the blood flow in the right leg differs greatly from that in the normal left leg, both in regard to onset and to extent. Within five minutes, the vasomotor tone begins to relax and, after 10 minutes, dilatation is well on its way. Within 15 minutes, the pulse volume has risen to 0.020 cc. and after 20 minutes, body heating reaches values round about 0.030 cc., that is, at a time when in the left leg the vessels are still fully constricted. The digital volume is the first to rise, and after 20 minutes has increased by fully 1.8 cc. At the same time, the rate of arterial inflow reaches 180 cc. per minute for 100 cc. of tissue.

As is very well illustrated in figure 4, re-

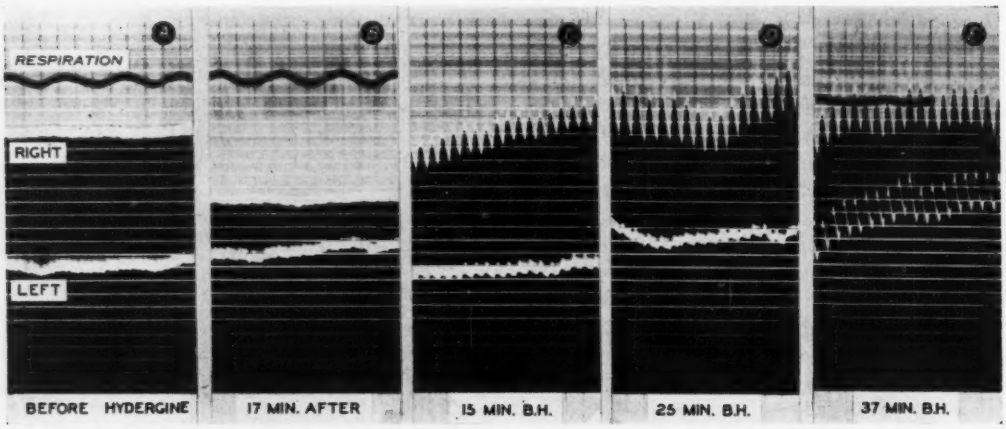

FIG. 5. Cuttings of the plethysmogram obtained in the same case as depicted in the chart of figure 4. (*A*) Pulse volume before injection; (*B*) No effect from the intra-arterial injection; (*C*) After 15 minutes body heating: marked dilatation obtained in the right leg only; (*D*) twenty-five minutes after body heating: full dilatation of the vessels in the right leg but still hardly any response in the left and (*E*) thirty-seven minutes after body heating: vessels of the left leg dilated, indicating that the lack of response was not due to an organic involvement of the peripheral vessels.

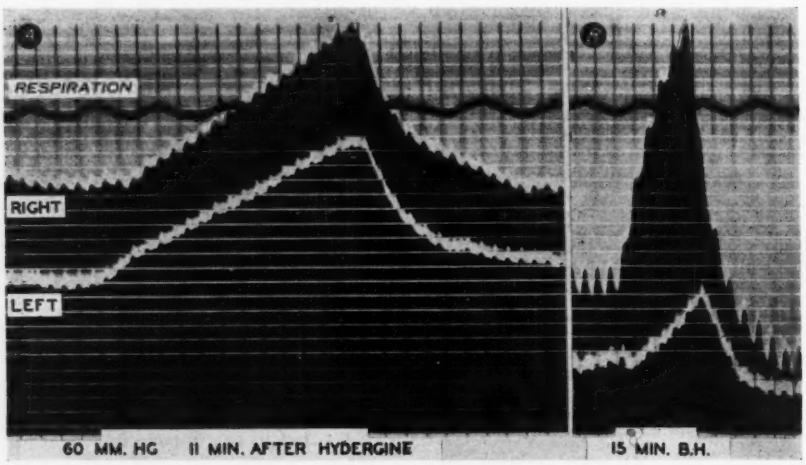

FIG. 6. (*A*) Venous congestion test 11 minutes after the injection of 0.5 mg. Hydergine into the right femoral artery. No difference in the gradient of the arterial inflow between the two limbs. (*B*) After additional 15 minutes body heating. Marked improvement in the blood flow of the right leg only.

flex dilatation not only occurs more readily but proceeds to a much higher level following the intra-arterial injection of Hydergine. By the time the vessels of the left limb start to dilate, those in the right have already dilated to a level far exceeding that eventually reached in the left leg.

The changes in height of the pulse volume are readily appreciated by consulting figure 5, which shows cuttings of the original plethysmogram. The upper tracing refers to the right, that is, the "pretreated" leg, and the lower to the "normal" left limb. The difference in the reaction is particularly well demonstrated 15

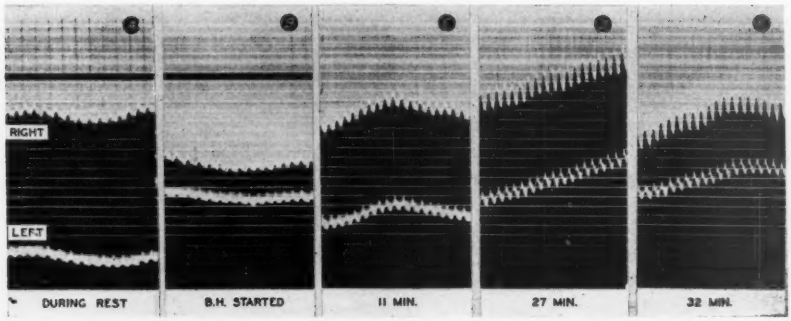

FIG. 7. Reflex dilatation of the vessels of the lower extremities in a patient who had an intra-arterial injection of Hydergine into the right femoral artery two days previously. There is still a difference in the response between the two legs.

and 25 minutes after the onset of body heating, when the difference in vasomotor tone is at its maximum, as judged by the difference in the height of the pulse volume. It is also well appreciated on recording the rate of arterial inflow by means of the venous congestion test (fig. 6).

How long following the injection can this difference in the response to reflex body heating following an intra-arterial injection of Hydergine be demonstrated? To answer this question, four patients were subjected to reflex body heating at various time intervals following the injection of Hydergine. In every one, the effect was still demonstrable after eight hours and in one fully 48 hours after the intra-arterial injection (fig. 7).

(3) *The Effect of an Intra-arterial Injection of Adrenalin following the Intra-arterial Injection of Hydergine:* As Goetz and Katz[14] demonstrated, the vasoconstrictor effect on the digital circulation of an intravenous or subcutaneous injection of adrenalin is not affected by a preceding *intravenous* injection of dihydroergocornine in man, whereas it is so in the cat.[16] It might be argued that the discrepancy between our results in man and those obtained in the animal were due to the higher concentration possible in the latter. Obviously, if such an effect could be demonstrated in man, it would be of some practical importance. The question was, therefore, reinvestigated following intra-arterial injection of Hydergine, when higher concentrations reach the peripheral vessels.

Five subjects were chosen in whom the intra-

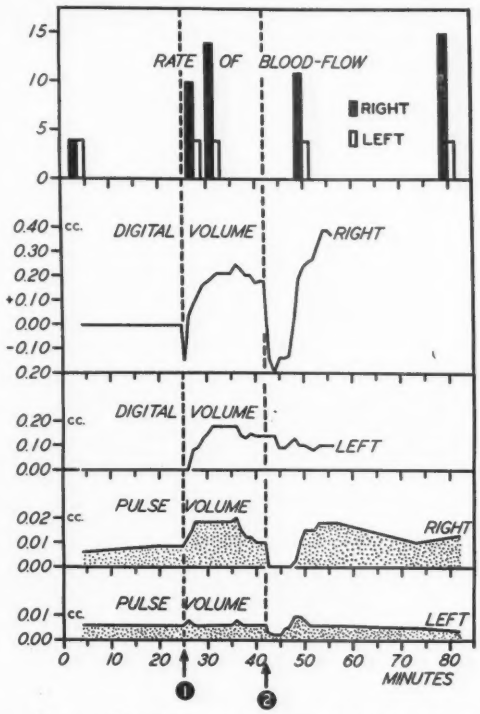

FIG. 8. The effect of intra-arterial adrenalin is not reversed by a preceding intra-arterial injection of Hydergine. At (*1*) Injection of 0.5 mg. Hydergine into the right femoral artery, producing an immediate response in the blood flow to the right leg; at (*2*) 0.10 mg. of adrenalin into the right femoral artery.

arterial injection of Hydergine produced an immediate peripheral vasodilatation. When this had reached its maximum and was well established, adrenalin was injected intra-

arterially. A typical response is illustrated in figure 8, which was obtained in a patient showing no signs of any cardiovascular disease or disorder. As can be seen, the injection of 0.5 mg. Hydergine into the right femoral artery produced an immediate increase in pulse volume, digital volume and the rate of arterial blood flow. Seventeen minutes after the intra-arterial injection, 0.10 mg. of adrenalin was injected intra-arterially into the same limb, which resulted in an abrupt and powerful constriction of the arterial tree. The pulse volume, which before varied around 0.01 cc., disappeared completely, the digital volume fell to well below the level recorded before the injection of dihydroergocornine and the arterial inflow on venous congestion could not be recorded. This constriction of the arterial tree was sustained for more than five minutes. When the blood vessels relaxed, the blood flow returned to the

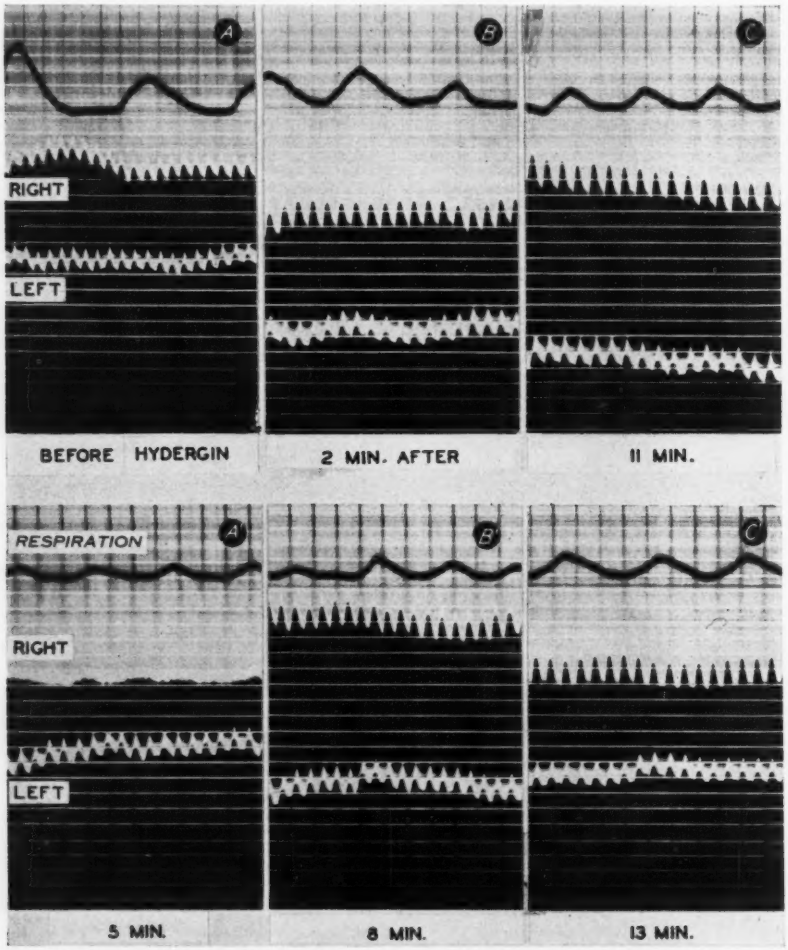

FIG. 9. Failure of intra-arterial Hydergine to modify the vasoconstrictor effect of a subsequent injection of adrenalin. Note, immediate dilatation following Hydergine (*B*) and vasoconstriction following injection of adrenaline resulting in the disappearance of the pulse volume (*A'*). Same case as figure 8. *B* and *C:* pulse volume after 0.5 mg. Hydergine into right femoral artery. *A'*, *B'* and *C'*: pulse volume 5,8 and 13 minutes after 0.1 mg. adrenalin into right femoral artery given 17 minutes after Hydergine.

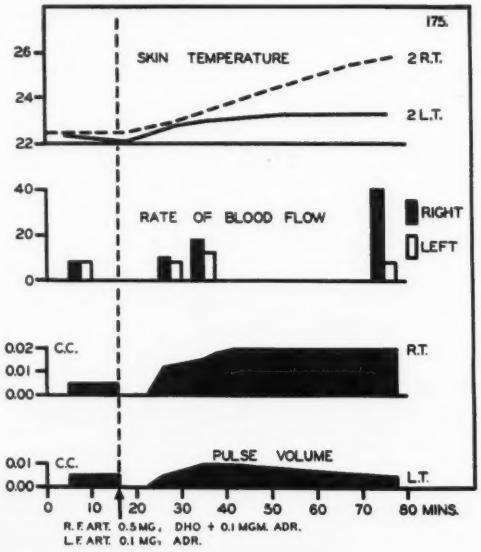

FIG. 10. Effect of an intra-arterial injection of a mixture containing both dihydroergocornine and adrenalin. The immediate effect is that of adrenalin only but the degree of reactive hyperemia in the right limb is not only infinitely greater but lasts throughout the time of investigation.

highest value recorded after the injection of Hydergine, and the degree of reactive hyperemia was far in excess of that normally seen. In the opposite limb, the effect of the intra-arterial adrenalin was only slight and less than it would have been, had the injection been by the intravenous route.

Both the degree of vasodilatation, obtained from the intra-arterial injection of Hydergine, and the degree of vasoconstriction, recorded during the subsequent injection of adrenalin, are very well appreciated by consulting the cuttings from the plethysmogram (fig. 9).

Similarly, vasoconstriction produced by subcutaneous or intravenous injection of adrenalin is not affected by preceding intra-arterial injection of Hydergine.

(4) *The Effect of an Intra-arterial Injection of a Mixture of Hydergine and Adrenalin:* We know from previous investigations[14] that dihydroergocornine does not affect the potency of adrenalin when mixed in vitro and given intravenously. This holds good for the intra-arterial route as well. In figure 10, 0.5 mg. dihydroergocornine plus 0.1 mg. of adrenalin were injected into the right femoral artery and the effect compared with an intra-arterial injection of 0.1 mg. of adrenalin, simultaneously administered in the left limb. Although the immediate reaction is the same in both limbs, that is, a complete arrest of the peripheral circulation for about five minutes, there is a difference when the circulation resumes. In the "normal" left leg, a moderate degree of reactive hyperemia is observed, the pulse volume and the rate of arterial inflow only temporarily assume a higher level and return to the original values within 30 minutes. In the right leg, however, in which Hydergine had been added, recovery is not only more rapid but the reactive hyperemia reaches a much higher level and the vessels go on to full dilatation and stay at that level, while under observation for the next 60 minutes. At the end of that time, the pulse volume in the right leg recorded 0.020 cc. as against 0.006 cc. in the left leg.

DISCUSSION

The results of the treatment of peripheral vascular diseases by the hydrogenated alkaloids of ergot have not been entirely satisfactory. Although these drugs are sympathicolytic in action, their effect on the peripheral vessels, when administered by the intravenous route, is unpredictable. In contrast, Bircher and Cerletti reported that, when given arterially, these drugs invariably produced peripheral vasodilatation in the cat, which seemed to fit in with the observations of Edwards and associates.[25] They state that the results from intra-arterial therapy are better than with any other type of treatment—excluding sympathectomy.

In our experience, the effect of the hydrogenated alkaloids of ergot is the same whether given by the arterial or by the venous route. Only in about half the patients did we record any peripheral vasodilatation following intra-arterial injection of Hydergine or dihydroergocornine, as judged by a rise in skin temperature, pulse volume and rate of arterial inflow, but failed in the remaining limbs to produce any visible effects. This failure was particularly striking when it occurred in patients with a high vasomotor tone, who, theoretically,

should be most responsive to the administration of sympathicolytic drugs. In this, our observations did not agree with the results of Bircher and Cerletti,[16] obtained in the anesthetized cat. However, this is not very surprising as it is well known that the results obtained in the animal cannot necessarily be transferred to man, particularly, when the sympathetic nervous system is involved.

Although it may be concluded that Hydergine had no effect in those cases where it failed to produce vasodilatation, this would be misleading. The intra-arterial injection of Hydergine did produce changes, most likely on the neurovascular apparatus, which are only revealed when we start dilating the vessels, either by body heating or by producing reactive hyperemia. We then discover that the vessels of the injected extremity respond sooner and to a greater degree to these procedures.

Rothlin[4] has already drawn attention to the fact that the various effects of the ergot alkaloids can be divided into two groups; those which are immediately visible and those which are latent and will only be apparent when the respective organ is stimulated. No doubt we are dealing here with the same type of reaction; the intra-arterial injection of Hydergine produces both, the immediately visible and latent or potential effects. Although in the past only the former effects have been considered, the latter are no less important on account of their therapeutic potentialities. It would appear that therapy with the hydrogenated alkaloids of ergot could be made more effective by combining the intra-arterial injection with other vasodilator procedures, notably body heating, but not necessarily applied to such a degree as to produce general vasodilatation throughout the body.

Vasodilator therapy suffers from one major disadvantage. If given by the oral, subcutaneous or intravenous route, dilatation, if effective, affects all vessels throughout the body. If all vessels are normal, as in many vascular "disorders," there is no harm in this. But if the resistance in one area, due to arterial "disease" or other reasons, should differ from the remainder, vasodilatation may affect the delicately balanced distribution of the blood considerably and may lead to a marked movement of blood from the area with the higher into that with the lower resistance. Consequently, vasodilator therapy in cases of arterial disease may achieve the exact contrary to what it sets out to do.

Intra-arterial instead of intravenous therapy obviously offers a way out of this dilemma. It is able to overcome some of the difficulties inherent in intravenous therapy with vasodilator and sympathicolytic drugs. Its advantages are the possibility of producing more powerful dilatation by virtue of the selective effect and the higher local concentration, achieved from smaller doses than are necessary with intravenous therapy. Thus, the effect of intra-arterial therapy is purely local, without dilatation in the rest of the body with its accompanying side-effects. In this, intra-arterial therapy can be compared with treatment by paravertebral block. However, it is obvious that unless such drugs which are to be given intra-arterially produce vasodilatation constantly, repeated arterial puncture will not be justified, and intra-arterial therapy has come in for some criticism in this respect.[26]

In a previous communication,[14] we reported that dihydroergocornine suppressed or reversed the rise in blood pressure, following the injection of adrenalin. Although we could not demonstrate a similar effect with respect to the effect of adrenalin on the peripheral vessels, Bircher and Cerletti[16] subsequently found that in the cat, Hydergine, when given intra-arterially, abolishes and reverses peripheral vasoconstriction normally produced by adrenalin. We have now confirmed our previous results and can state that Hydergine, when given intravenously or by the intra-arterial route, exhibits no adrenolytic action on the peripheral vessels in man.

Summary

The effect of intra-arterial Hydergine or dihydroergocornine on the peripheral blood vessels has been recorded and compared with the blood flow in the contralateral limb.

The immediate result is unpredictable, vasodilatation occurring in about half of the cases. In none of our cases was there ever any direct

vasoconstrictor action recorded. In principle, the effect was, therefore, the same as after an intravenous injection.

Although the intra-arterial injection of the hydrogenated alkaloids of ergot may not produce any visible effects on the peripheral blood vessels, the injection has not been without effect, as it does change their responsiveness to the release of the central vasoconstrictor tone. It was found that after an intra-arterial injection of Hydergine, reflex vasodilatation, as produced by body heating, occurs considerably earlier and proceeds to higher levels than in the contralateral normal limb.

The intra-arterial injection of the hydrogenated alkaloids of ergot produces, therefore, both visible and potential changes in the peripheral blood vessels. The potential changes can be demonstrated for many hours following the original injection and are of considerable therapeutic interest.

The vasoconstrictor effect of adrenalin on the peripheral blood vessels is not affected by preceding intra-arterial injections of Hydergine or dihydroergocornine. It is, therefore, confirmed that in man the hydrogenated alkaloids of ergot have no adrenergic properties in respect to the peripheral circulation.

The reactive hyperemia, observed following the temporary arrest of the peripheral circulation as produced by adrenalin, is greater and more lasting if this was preceded by an intra-arterial injection of Hydergine or dihydroergocornine.

In some respects, the results are contrary to observations made in the animal. This stresses the caution which has to be exercised, in trying to apply to man results obtained in animal experiments.

The special merits of intra-arterial, as opposed to intravenous therapy, are discussed with special reference to the treatment of cases of peripheral vascular diseases.

Acknowledgment

Part of these investigations were carried out at the Medizinische Poliklinik of the University of Bern, Switzerland through the hospitality received from Professor W. Hadorn. The author is deeply grateful for valuable assistance received in this work from Dr. P. Baumgartner of the Medizinische Poliklinik.

I wish to thank Sandoz Ltd., Basel, Switzerland, for generous supplies of Hydergine and dihydroergocornine.

The technical assistance of Miss R. Jones and Mr. C. C. Goosen is gratefully acknowledged.

Summario in Interlingua

Le effecto immediate del hydrogenate alkaloides de ergota, si administrate intra-arterialmente, es inpredicibile. Vasodilatation es obtenite solmente in certe patientes. Tamen, il esseva constatate que in le casos que non reage per vasodilatation le vasos responde plus facilemente al relaxation del tono sympathic, lo que prova que le droga habeva nonobstante un effecto (potential) probabilemente super le apparato neurovascular. Iste effecto esseva demonstrabile durante multe horas e es consequentemente de alte interesse therapeutic.

Mesmo in le plus alte concentrationes local que es possibile per le administration intra-arterial, le hydrogenate alkaloides de ergota non exhibiva ulle action adrenolytic super le peripheric vasos sanguinee de humanos.

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Clinical Studies on Involvement of the Pulmonary Artery by Syphilitic Aortic Aneurysms

By JOHN J. DONNELL, M.D., DAVID C. LEVINSON, M.D. AND GEORGE C. GRIFFITH, M.D.

Cardiac catheterization and angiocardiography studies are reported in two patients with syphilitic aortic aneurysms, both of which compromised the pulmonary circulation. In the first instance the right main pulmonary artery was compressed and pulmonary hypertension proximal to the compression resulted. In the second patient the aneurysm ruptured into the pulmonary artery producing an aortic-pulmonary fistula. This patient also had pulmonary hypertension and evidence at cardiac catheterization of a large left-to-right shunt. The difficulty of making the clinical diagnosis of pulmonary artery compression by an aortic aneurysm is discussed. Cardiac catheterization and angiocardiography were essential for establishing this diagnosis in life.

THE purpose of this report is to describe two cases of syphilitic aortic aneurysm, each of which compromised the pulmonary artery circulation. In one case, the aneurysm created chronic cor pulmonale by obstructing the pulmonary artery with extrinsic pressure; in the other case, the aneurysm ruptured into the pulmonary artery, producing a chronic aortic-pulmonary fistula. Despite the frequency of syphilitic aortic aneurysms, the above complications have been rarely diagnosed during life.

Usually, involvement of the pulmonary circulation becomes apparent at the time that the aneurysm ruptures into the pulmonary artery. Clinically, this event is acute and disastrous as a rule, but occasionally the rupture may occur with survival and present signs suggesting patent ductus arteriosus.[1-3] Nicholson[4] in 1943, reviewed the literature, consisting of 81 reported cases, and added two cases of rupture of syphilitic aortic aneurysm into the pulmonary artery. Subsequently, additional cases have been reported.[5, 6] More than likely, most cases of this type are preceded by pulmonary artery compression.[3] In 1939, Garwin and Siegal[8] reported three cases of cor pulmonale due to compression of the pulmonary artery without rupture of the aneurysm. In these instances, death resulted from what appeared to be right sided heart failure. Later, Eichler and Heller[9] and Pearson and Nichol[10] reported similar cases. Under any circumstance, the diagnosis is a difficult one, as indicated by the latter authors. Abrahams and Wood[11] reported a case thought preoperatively to have pulmonary stenosis, who had positive serology as well. At surgery, an unidentified obstruction was found within the pulmonary artery along with hypertension proximal to the obstruction. An aortic aneurysm was not identified.

The following cases are thought to be of interest because the diagnoses were made clinically and verified by both cardiac catheterization and angiocardiography.

From the University of Southern California School of Medicine, Department of Medicine (Cardiology), and the Los Angeles County Hospital, Los Angeles, Calif.

CASE REPORT

Case 1: The patient was a 38-year-old Negro man, admitted to the Los Angeles County Hospital on Nov. 7, 1951 because of left anterior chest pain of six months' duration. The pain had become more severe during the previous two months, and he had observed aggravation by coughing and sneezing. Some relief was afforded by resting in the supine position. He had noted shortness of breath only when the pain was especially severe. There was a history of penile chancre at the age of 17, which healed spontaneously. Incidental discovery of positive serology at the age of 32 resulted in "a few" injections, thought to be penicillin. At the age of 25 he was injured in an automobile accident, which he thought resulted in fractures of "several ribs" on the right side.

The patient was a well developed, well nourished Negro, complaining of chest pain, but was not

acutely ill. The blood pressure was 140/70 mm. Hg in the right arm and 135/56 in the left arm. Radial pulses were equal and normal in volume. The pupils were normal, and eyegrounds were negative. A systolic pulsation in the suprasternal notch was noted. A tracheal tug was not present. An area of systolic expansile pulsation 2 by 3 cm. in size could be seen in the second left intercostal space about 3 cm. from the sternal border, and a systolic thrill was palpable at this point. The point of maximum impulse was in the fifth intercostal space at the midclavicular line; the left border of cardiac dullness extended about 1 cm. lateral to this point. Both heart sounds were heard at all valve areas, and the second pulmonic was louder than the second aortic sound. A grade III systolic murmur was described at the pulmonic area, and a faint diminuendo diastolic murmur was heard along the left sternal border. The heart rate was 80 beats per minute, with a regular rhythm interrupted occasionally by premature contractions. The lungs were clear. The examination of the abdomen was negative. A penile scar was noted. No dependent edema was present, and peripheral pulsations were unimpaired. No neurological abnormality was demonstrable.

Hemoglobin was 14 Gm. per 100 cc. There were 9800 white blood cells per cubic millimeter. Urinalysis was negative. The Wassermann was strongly positive. Examination of spinal fluid gave negative serology and colloidal gold; protein was 38 mg. per 100 cc.

Roentgenogram of chest showed an aneurysm of the ascending aorta and arch (fig. 1). The electrocardiogram showed right axis deviation in a vertical type heart.

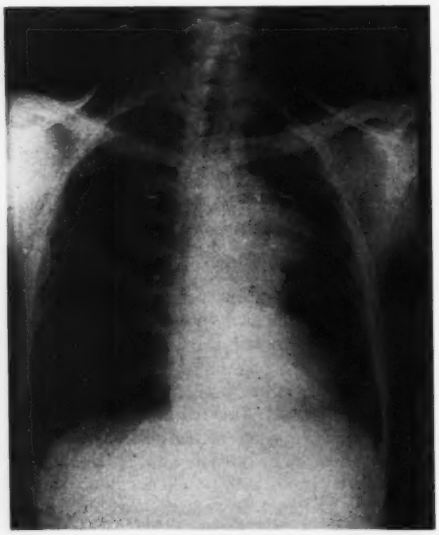

FIG. 1. (Case 1): Posterior-anterior chest x-ray film.

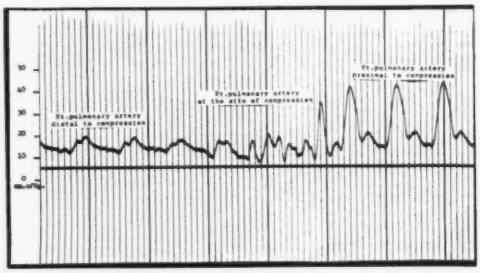

FIG. 2. (Case 1) Right pulmonary pulse pressure contour showing a drop in pulmonary artery pressure distal to the point of compression by aneurysm.

Cardiac Catheterization: Under local anesthesia a No. 8 French cardiac catheter was introduced into the left basilic vein in the median antecubital space and passed successively under fluoroscopic guidance into the superior vena cava, right atrium, right ventricle, main pulmonary artery and right pulmonary artery. An abrupt rise in pressure was noted as the catheter was being withdrawn from the right pulmonary artery toward the main pulmonary artery. This maneuver was repeated several times, and the same pressure change occurred constantly (fig. 2).

Data obtained by cardiac catheterization have been tabulated in table 1. The findings at cardiac catheterization established moderate right ventricular hypertension, hypertension of the main pulmonary artery, and "acquired stenosis" of the right pulmonary artery, with reduced pressure distal to compression by the aneurysm.

Angiocardiogram: With the patient in the supine position, 50 cc. of 70 per cent Neo-iopax was rapidly injected into the left basilic vein and six x-ray exposures obtained at two-second intervals. The dye entered the superior vena cava, right atrium, right ventricle and the main pulmonary artery. The dye passed into the left pulmonary artery, but the right pulmonary artery did not fill (fig. 3). The aneurysm and the left ventricle were well visualized (fig. 4). Angiocardiography confirmed that a large aneurysm of the aortic arch was obstructing the main right pulmonary artery.

Follow-Up: On March 28, 1952, the patient was readmitted for the purpose of wiring the aneurysm. By the cutaneous route, 100 feet of No. 32 wire were inserted into the aneurysmal sac. One week later, 200 feet more were inserted, and the patient was discharged subsequently.

On Feb. 18, 1953, he returned to the hospital because of a perirectal abscess. This required incision and drainage, and was later excised. At that time, he had no complaints which were related to his aneurysm, and his physical findings were essentially

TABLE 1.—*Findings at Cardiac Catheterization*

Case 1

Station	B.P. (mm.Hg)	Oxygen		Additional Data
		Vol. (%)	Saturat. (%)	
Superior Vena Cava	3/1	10.4	59.3	O_2 Cap. 17.6 vol.%
Right Atrium (Mid)	3/1	10.1	57.6	O_2 Cons. 180 cc./min.
Right Atrium (High)	3/1	10.7	60.6	Cardiac Output 3.6 L./min.
Right ventricle	50/7	10.2	58.0	
Main Pulmonary Artery	50/12	9.6	54.6	
Right Pulmonary Artery (Proximal to stenosis)	40/14	10.1	57.5	
Right Pulmonary Artery (Distal to stenosis)	15/8			
Femoral Artery		14.6	82.9	

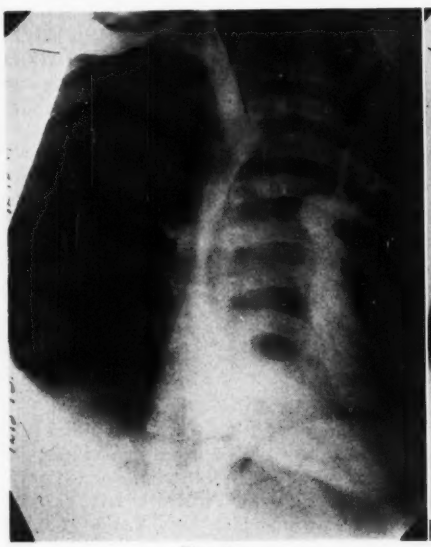

FIG. 3

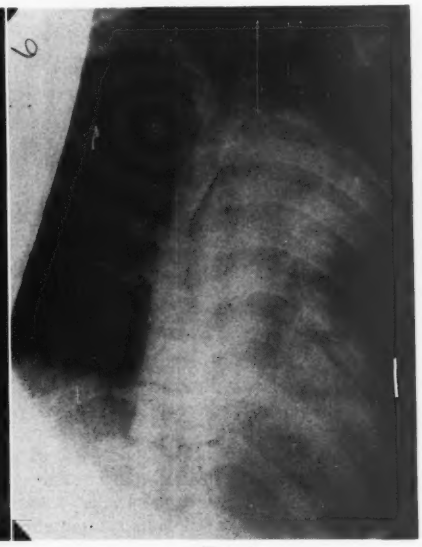

FIG. 4

FIG. 3. (Case 1): Posterior-anterior angiocardiogram showing dye in right atrium, right ventricle, main pulmonary artery and left pulmonary artery with nonvisualization of the right pulmonary artery.

FIG. 4. (Case 1): Posterior-anterior angiocardiogram showing visualization of the left ventricle and aortic aneurysm 12 seconds after injection of the dye.

unchanged. The systolic thrill and murmur were described, but no diastolic murmur was found. The blood pressure was recorded at 120/70. The chest x-ray and electrocardiogram were unchanged.

Case 2: A 46-year-old Negro woman entered the hospital on April 13, 1954, with the chief complaints of dyspnea, orthopnea and swelling of the legs and abdomen. Onset of her present illness occurred in August, 1953, at which time she developed paroxysmal episodes of dyspnea with wheezing, associated with "sickness" in the upper abdomen. These attacks were brief in duration, sudden in onset and cessation, and seemed to be initiated by assuming the left lateral decubitus position. There was no relation of their onset to effort. In between these episodes she felt well, except for persistent anorexia with resultant weight loss. In November, 1953, she was forced to discontinue her occupation as a domestic. Swelling of the ankles and exertional dyspnea first were noted in Jan., 1954, progressing to dyspnea at rest, orthopnea and marked swelling of the legs and abdomen by April, 1954. There was no history of a heart murmur, cyanosis, rheumatic fever or syphilis.

The patient was a normally developed, but emaciated, orthopneic Negress who was severely dyspneic,

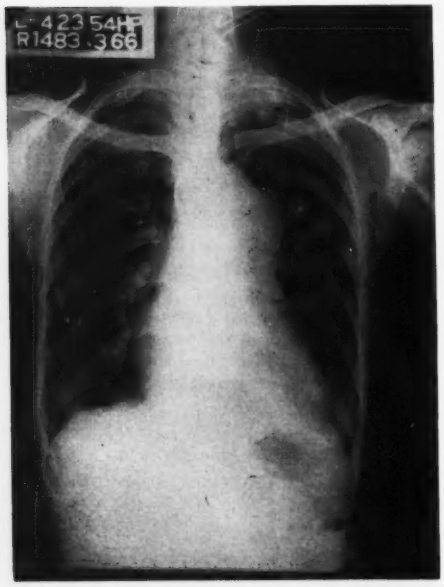

FIG. 5. (Case 2): Posterior-anterior chest x-ray film.

and preferred to lie on her right side. Her voice was quite hoarse. The pupils were round, equal and normally reactive to light and accommodation. The neck veins were distended in the upright position. The trachea was displaced slightly to the left, and a prominent tracheal tug was noted. A systolic lift of the upper sternum was apparent, unassociated with localized pulsation or a well identified point of maximum impulse. A systolic thrill, felt maximally at the third and fourth left intercostal spaces, was transmitted widely over the precordium. Impaired resonance was found at the manubrium, along with a widening in the upper mediastinum on percussion. The left border of cardiac dullness extended about 9 cm. to the left of the mid-sternal line in the fifth intercostal space. Valve sounds were normal at all areas, except for splitting and accentuation of the pulmonic second sound. A continuous murmur with systolic accentuation, best heard at the fourth left intercostal space next to the sternum, was transmitted widely over the chest, but especially into the left infraclavicular area and axilla. The systolic component was grade IV to V in intensity. The cardiac rhythm was regular at a rate of 120 beats per minute. The blood pressure was 180/80-0 mm. Hg in each arm, and the pulse was Corrigan (water-hammer) in quality. Decreased resonance was found in the right lung base, along with bilateral basal crepitant rales. Sonorous rales and wheezes were confined to the left posterior chest, and there was accentuation of these sounds during cardiac systole; this phenomenon was accentuated when the patient was tilted toward the left, during which maneuver a paroxysm of coughing occurred. Free fluid was demonstrable in the abdomen, and a tender liver was palpable four cm. below the right costal margin.

Hemoglobin was 11 Gm. per 100 cc. There were 7400 white blood cells per cubic millimeter. Urinalysis was negative. The Wassermann reaction was strongly positive.

Roentgenogram of chest showed grade I left ventricular enlargement and aneurysm of the arch and first portion of the descending thoracic aorta (fig. 5). An electrocardiogram was suggestive of early left ventricular hypertrophy.

Response to specific cardiotherapy was satisfactory. With restoration of cardiac compensation, 27 pounds of edema fluid were eliminated. Dyspnea and orthopnea disappeared, but the patient continued to prefer to lie on the right side. The blood pressure spontaneously reduced to 118/50-30 mm. Hg.

Cardiac Catheterization: Under local anesthesia a No. 7 French cardiac catheter was introduced into the median basilic vein in the left antecubital fossa and passed under fluoroscopic guidance successively through the superior vena cava, right atrium, right ventricle, main pulmonary artery, and finally into the right peripheral pulmonary artery. Pressures and blood samples were taken at these stations. An attempt was made to insert the catheter into the left lung field, but it could not be passed beyond the left main pulmonary artery. Data obtained by cardiac catheterization have been tabulated in table 2. The findings at cardiac catheterization established (1) definite evidence of a left to right shunt into the pulmonary artery and (2) elevation of pressures in the right ventricle, pulmonary artery, and wedged peripheral pulmonary artery, probably secondary to left ventricular failure.

Angiocardiograms: Two studies were carried out, the first in the anterior-posterior projection and the second in the left oblique. In both studies, 50 cc of 70 per cent Neo-iopaz was rapidly injected into the left basilic vein. In the anterior-posterior projection films were exposed at the rate of one per second. Neo-iopax passed readily into the right pulmonary artery, but the left pulmonary artery was compressed by a large mass (fig. 6). In the left oblique view exposures were at the rate of two per second. Radiopaque material was visible in the main pulmonary artery and in branches of the right pulmonary artery (fig. 7). Dye was not visualized in the left lung field. Also a dilated and elongated arch was apparent with aneurysmal dilatation of the first portion of the descending aorta. At approximately 12 seconds after the dye was injected, it was visualized in the arch of the aorta (fig. 8).

These studies confirmed the diagnosis of a chronic aortic-pulmonary fistula, resulting from the rupture of a syphilitic aortic aneurysm into the pulmonary

TABLE 2.—*Findings at Cardiac Catheterization*

Case 2

Station	Pressure (mm.Hg)	Oxygen		Additional Data
		Vol. (%)	Saturat. (%)	
Superior Vena Cava	8/0	8.63	30.59	O_2 Cap. 17.06 vol.%
Right Atrium (Mid)	8/0	7.85	46.01	O_2 Cons. 125 cc./min.
(Low)		8.93	52.35	Systemic blood flow 1.7 L./
Right Ventricle (Body)	85/7	8.39	49.18	min.
(Conus)		7.85	46.01	Shunt flow 6.5 L./min.
Main Pulmonary Artery	80/35	13.24	77.61	Cardiac Output 8.2 L./min.
Right Pulmonary Artery	75/32	12.63	74.03	
Left Pulmonary Artery	85/32	12.64	74.68	
Right Peripheral Pulmonary Artery	25/20	13.45	78.84	
Right Femoral Artery		15.29	89.62	

FIG. 6. (Case 2): Posterior anterior-angiocardiogram showing dye in the main pulmonary artery and compression of the left pulmonary artery by the aneurysm.

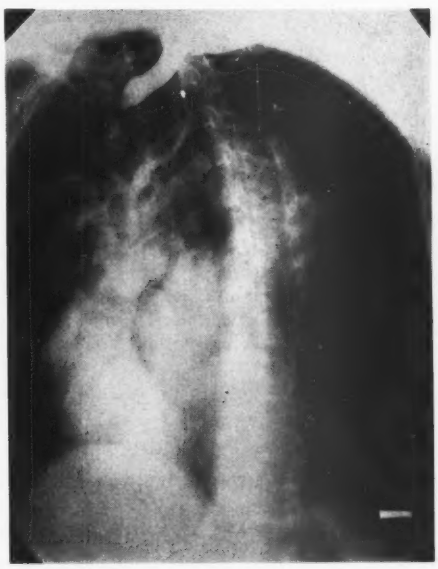

FIG. 7. (Case 2): Posterior-anterior angiocardiogram in the left oblique view showing dye in the main pulmonary artery and in branches of the right pulmonary artery with non-visualization of the branches of the left pulmonary artery.

artery. Exploratory thoracotomy was performed on May 6, 1954. The following is a report of the surgery and findings.

Under general anesthesia, the patient was placed on the right side and a parascapular incision was make in the skin. Dissection was carried down through the subcutaneous tissue and chest muscle to expose the ribs. The fifth rib was resected subperiosteally and pleural space entered. Mediastinal pleura overlying the aneurysm and pulmonary artery was opened and dissection carried out around the aorta and pulmonary artery to a point where any further resection would have resulted in a massive bleeding. There was marked fusiform dilatation of the ascending and transverse arch. The beginning descending aorta was about 4 to 5 times normal in size. A marked thrill was felt over the pulmonary artery which could be obliterated by closing off the left pulmonary artery. The pulmonary artery was also markedly dilated and there was marked inflammatory reaction between aorta and pulmonary artery,

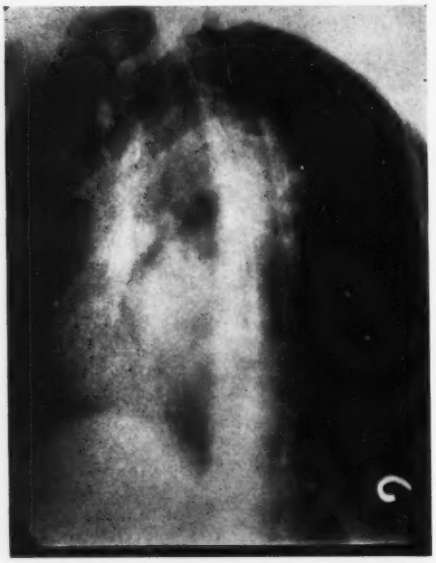

FIG. 8. (Case 2) Posterior-anterior angiocardiogram in the left oblique view showing visualization of the left ventricle and aortic arch at 12 seconds.

apparently due to syphilis. This area extended from the left subclavian artery for a distance of 5 cm. down the descending aorta. Because of the extensive inflammatory reaction and the size of the fusiform aneurysm of the aorta, nothing surgically could be done in this case.

DISCUSSION

The difficulty in making the clinical diagnosis of pulmonary artery compression by an aortic aneurysm is confirmed by the few clinical reports in the literature. In a patient who has an aortic aneurysm accompanied by aortic insufficiency, the clue to pulmonary artery compression may be found in the electrocardiogram. The presence of right axis, or combined right and left ventricular hypertrophy should arouse the suspicion that the aneurysm may be compressing a pulmonary artery. In case 1, the presence of right axis in the electrocardiogram led to the definitive diagnosis being made by cardiac catheterization and angiocardiography.

In case 2, the presence of a syphilitic aortic aneurysm, coupled with findings suggesting a patent ductus arteriosus or aortic-pulmonary defect, made the diagnosis seem obvious. Although rupture of an aortic aneurysm into either of the heart chambers or great vessels may produce this same murmur and thrill, individual features characterizing the various sites of rupture exist. Herrmann and Schofield have emphasized these individual features, and have delineated the specific syndrome of rupture of an aortic root-aneurysm into the right atrium.[12] Cardiac catheterization produced conclusive evidence of a left to right shunt into the pulmonary artery in this case, and angiocardiography revealed compression with displacement of the left main pulmonary artery. These findings were also confirmed by a thoracotomy.

SUMMARY

Two cases of syphilitic aortic aneurysm are presented, each involved the pulmonary artery. Cardiac catheterization and angiocardiography were essential in establishing the specific abnormalities present in each case. These two techniques are well suited to the study and clarification of such problems. We are unable to find any previous reports wherein such an opportunity presented itself. As the prospect for surgical correction of such complications improves, the need for accurate diagnosis increases.

SUMMARIO IN INTERLINGUA

Es reportate studios de catheterisation cardiac e de angiocardiographia in duo patientes con syphilitic aneurysmas aortic compromittente le circulation pulmonar. In le prime caso le major arteria dextero-pulmonar esseva comprimite con le resultato de hypertension pulmonar in le segmento cis-compressional. In le secunde caso le aneurysma se rumpeva a in le arteria pulmonar con le resultato de un fistula aortico-pulmonar. In iste caso hypertension pulmonar esseva etiam constatate, e le catheterisation cardiac revelava signos del presentia de un considerabile derivation sinistro-dextere. Es discutite le difficultate de establir le diagnose de compression pulmono-arterial per aneurysma aortic. Nos trovava que catheterisation cardiac e angiocardiographia esseva indispen-

sabile pro establir iste diagnose durante le vita del patiente.

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The Influence of the Sex Hormones on the Circulating Lipids and Lipoproteins in Coronary Sclerosis

By M. F. Oliver, M.B., M.R.C.P. (Edinburgh) and G. S. Boyd, Ph.D.

The administration of ethinyl estradiol to 100 survivors of myocardial infarction resulted in uniform correction of the abnormal circulating lipid and lipoprotein concentrations. Gynecomastia and depression of libido were well tolerated by the patients but were not ameliorated by an androgen preparation nor by a progesterone analogue. Methyl testosterone, which partly inhibited the estrogen effect, increased the concentration of cholesterol on the beta lipoprotein fraction. Progesterone had no significant effect on the circulating lipids and lipoproteins. Assessment of the effect of ethinyl estradiol on human atherogenesis must depend on long-term evaluation of its influence on morbidity and mortality rates.

DURING the fourth and fifth decades of life, the clinical manifestations of coronary sclerosis are impressively more frequent in men than in women. So long as their reproductive physiology is maintained, women apparently enjoy some protection from the development of clinical coronary disease. There are abnormalities of the circulating lipids[1-3] and lipoproteins[4-7] in association with clinical coronary disease, and during the menstrual cycle there are cyclical variations in the circulating lipids and lipoproteins. It has been suggested that the physiologic depression at ovulation of plasma total cholesterol and the plasma total-cholesterol:phospholipid ratio (the C/P ratio) might be due to endogenous estrogen secretion.[8] Corresponding fluctuations occur in the distribution of cholesterol between the alpha and beta lipoprotein fractions during the menstrual cycle.[9] The administration of an oral estrogen to subjects with clinical coronary disease has resulted in considerable rectification of the abnormalities in the circulating lipid and lipoprotein patterns.[10-14]

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This report, which elaborates this effect of the estrogenic hormones and describes the influences of androgens and progestins, is part of a comprehensive study of the hormonal factors which may be involved in the homeostasis of the circulating lipids and lipoproteins, and of lipid metabolism.

Methods and Results

All the subjects were men whose ages ranged from 32 to 64 years, and all had electrocardiographic proof of myocardial infarction. A large majority of the men were in full employment and visited the Department of Cardiology in the Edinburgh Royal Infirmary during their working day. They attended at the same time at each visit and were not fasting or subject to any dietary restrictions, unless there was associated obesity. With the exception of the long-term ethinyl estradiol study, for which the selection of cases followed a separate pattern, all the subjects were hypercholesterolemic and at least three months had elapsed between the time of the infarct and the start of the investigation. Plasma total cholesterol was estimated by the Schoenheimer-Sperry procedure as modified by Sperry and Webb.[15] Plasma lipid phosphorus was estimated by the molybdenum blue method of Allen.[16] The distribution of cholesterol between the lipoprotein fractions was estimated by the zone electrophoresis method of Boyd;[17] the percentage distribution of cholesterol between the alpha and beta lipoprotein fractions was expressed as a ratio, the α:β lipoprotein ratio.

The investigations have been divided into five groups.

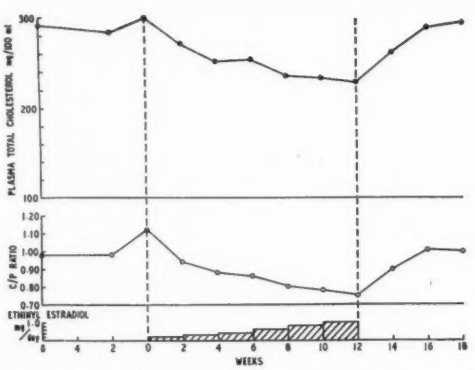

FIG. 1. The effect of ethinyl estradiol on the plasma lipids of 15 hypercholesterolemic men with coronary disease. The dose was gradually increased from 200 μg. to 1 mg. daily over 12 weeks.

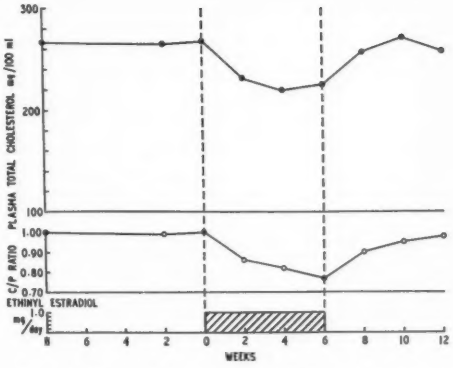

FIG. 2. The effect of ethinyl estradiol on the plasma lipids of 30 hypercholesterolemic men with coronary disease. One mg. was administered daily for six weeks.

(1) *Ethinyl Estradiol*

(a) *Graduated Study.* Fifteen men received daily 200 μg. of ethinyl estradiol (British Schering) for two weeks, then 300 μg. for the next two weeks and then 400 μg. for the next two weeks. The daily dose was then increased by 200 μg. every two weeks until the men had received 1 mg. daily for a period of two weeks after which ethinyl estradiol was withdrawn.

This study was continued for six more weeks after ethinyl estradiol was withdrawn. The results of this study are shown in figure 1. The plasma total cholesterol fell from 300 mg. per 100 cc. to 230 mg. per 100 cc. after 12 weeks, a fall of 23 per cent ($p < 0.01$) and the total-cholesterol:phospholipid ratio from 1.12 to 0.75, a fall of 33 per cent ($p < 0.01$). The serum alpha:beta lipoprotein ratio rose from 7:93 to 15:85 (table 1). Following the withdrawal of ethinyl estradiol these values rapidly returned to their pretreatment levels, and not infrequently there occurred a rebound above the values prevailing during the control period.

(b) *Large Dose Study.* Thirty men received 1 mg. of ethinyl estradiol daily for six weeks and were followed for a further six weeks after this had been withdrawn. The results of this study are shown in figure 2. The plasma cholesterol fell from 268 mg. per 100 cc. to 225 mg. per 100 cc. after six weeks, a fall of 16 per cent ($p < 0.02$), and the total-cholesterol:phospholipid ratio fell from 1.00 to 0.77, a fall of 23 per cent ($p < 0.01$). The serum alpha:beta lipoprotein ratio rose from 9:91 to 14:86 (table 1).

(c) *Long-Term Study.* This investigation differed from the others in that the principal object was an attempt to assess the effect of ethinyl estradiol on the morbidity and mortality rates in men who were admitted to hospital following their first myocardial infarct; the results of this aspect of this long-term study will be reported in full when the series is larger and more time has elapsed. Between four and six weeks after discharge from hospital, alternate cases received either tablets containing 200 μg. of ethinyl estradiol or identical inert tablets. In each group 25 men have been followed for 3 months, 20 men for 6 months, 16 men for 9 months, 10 men for 12 months and 6 men for 15 months. As the subjects were consecutive admissions, not all were hypercholesterolemic, although they all showed some abnormality of their circulating lipids or lipoproteins.

The results of this study are shown in figure 3. In the group receiving ethinyl estradiol, the plasma total cholesterol fell from 255 mg. per 100 cc. to 222 mg. per 100 cc. 15 months later, a fall of 13 per cent; the total-cholesterol:phospholipid ratio fell from 0.97 to 0.68 15 months later, a fall of 30 per cent and the alpha:beta lipoprotein ratio rose from 9:91 to 18:82 after six months (table 1). In the group receiving inert tablets, the plasma total cholesterol fell from 239 mg. per 100 cc. to 224

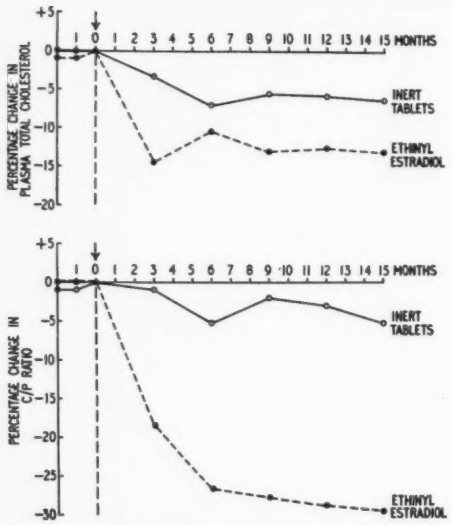

FIG. 3. The percentage change in the plasma lipids during the administration of 200 μg. of ethinyl estradiol daily for 15 months.

mg. per 100 cc. 15 months later, a fall of 6 per cent; the total-cholesterol:phospholipid ratio fell from 0.95 to 0.90 15 months later, a fall of 5 per cent, and the alpha:beta lipoprotein ratio changed from 10:90 to 9:91 after six months (table 1).

TABLE 1.—*The Changes in the Percentage Distribution of Cholesterol Between the Alpha and Beta Lipoprotein Fractions Produced By Various Sex Hormones*

	No. of Men	α:β Lipoprotein Ratio		
		Control	End of course	After course
Ethinyl estradiol				
(a) Graduated study	15	7:93	15:85	9:91
(b) Large dose study	30	9:91	14:86	9:90
(c) Long-term study				
Active preparation	20	9:91	18:82	After 6 months
Inert preparation	20	10:90	9:91	
Estradiol				
(a) 12 mg. daily	3	12:88	19:81	11:89
(b) 24 mg. daily	3	10:90	14:86	7:93
Estrone				
(a) 30 mg. daily	3	14:86	12:88	6:94
(b) 50 mg. daily	3	13:87	11:89	9:91
Hexestrol	6	10:90	14:86	9:91
Methyl testosterone	6	13:87	6:94	6:94
Progesterone	6	9:91	11:89	8:92

The majority of the 100 men who have received ethinyl estradiol experienced gynecomastia, which at first caused some concern to a few but was generally very well tolerated. Depression or loss of libido was not uncommon, but caused acute distress in only one case. Nausea occurred occasionally and caused the withdrawal of the estrogen in two cases; these subjects were excluded from the studies. Angina occurred more readily and more severely in two men and ethinyl estradiol was withdrawn from them both, and they were also excluded from these studies.

(2) *The Naturally Occurring Estrogens*

Although the potency of these estrogens is comparatively low when administered orally, this route was chosen for the convenience of the subjects.

(a) *Estradiol.* Three men received 12 mg. of estradiol (Ciba) orally each day for 14 days. The results of this study are shown in figure 4. The plasma total cholesterol fell from 259 mg. per 100 cc. to 237 mg. per 100 cc. after 14 days, a fall of 8 per cent, and the total-cholesterol:phospholipid ratio fell from 0.95 to 0.87, a fall of 8 per cent. The alpha:beta lipoprotein ratio rose from 12:88 to 19:81 (table 1).

Three men received 24 mg. of estradiol orally each day for 14 days. The results of this study are shown in figure 5. The plasma total cholesterol fell from 260 mg. per 100 cc. to 228 mg. per 100 cc. after 14 days, a fall of 12 per

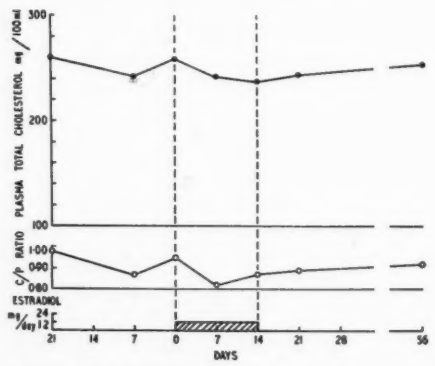

FIG. 4. The effect of estradiol on the plasma lipids of three hypercholesterolemic men with coronary disease. Twelve mg. were administered daily for 14 days.

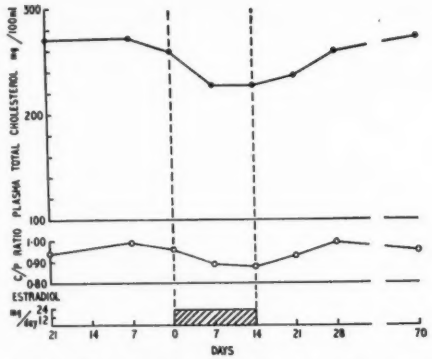

FIG. 5. The effect of estradiol on the plasma lipids of three hypercholesterolemic men with coronary disease. Twenty-four mg. were administered daily for 14 days.

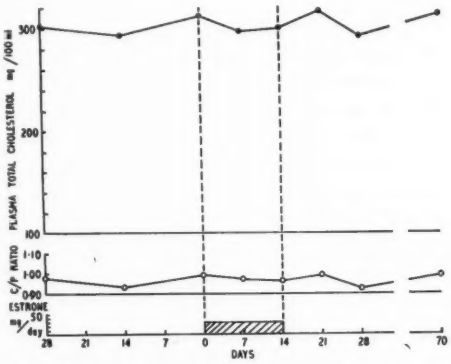

FIG. 6. The effect of Estrone on the plasma lipids of three hypercholesterolemic men with coronary disease. Thirty mg. were administered daily for 14 days.

cent, and the total-cholesterol:phospholipid ratio fell from 0.96 to 0.88, a fall of 8 per cent. The alpha:beta lipoprotein ratio rose from 10:90 to 14:86 (table 1).

(b) *Estrone.* Three men received 30 mg. of estrone (Organon) orally each day for 14 days. The results of this study are shown in figure 6. The plasma total cholesterol fell from 312 mg. per 100 cc. to 300 mg. per 100 cc. after 14 days, a fall of 3 per cent, and the total-cholesterol:phospholipid ratio fell from 0.99 to 0.96, a fall of 3 per cent. The alpha:beta lipoprotein ratio fell from 14:86 to 12:88 (table 1).

Three men received 50 mg. of estrone orally each day for 14 days. The results of this study are shown in figure 7. The plasma total cholesterol fell from 286 mg. per 100 cc. to 261 mg. per 100 cc. after 14 days, a fall of 9 per cent, and the total-cholesterol:phospholipid ratio remained constant at 0.94. The alpha:beta lipoprotein ratio fell from 13:87 to 11:89 (table 1). Despite the lack of response to estrone while it was being administered, a slight rebound occurred in the plasma total cholesterol which rose to 300 mg. per 100 cc. two weeks after estrone was withdrawn; the total-cholesterol:phospholipid ratio rose to 1.03 at that time, but there was no rebound in the alpha:beta lipoprotein ratio.

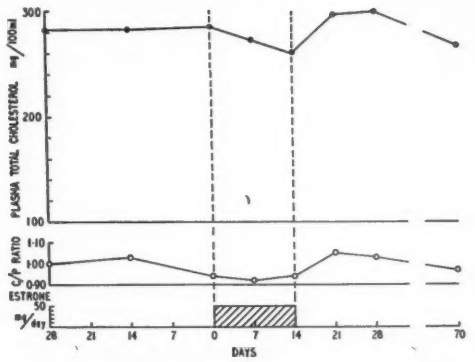

FIG. 7. The effect of estrone on the plasma lipids of three hypercholesterolemic men with coronary disease. Fifty mg. were administered daily for 14 days.

(3) *Hexestrol*

Six men received 60 mg. of hexoestrol (British Drug Houses) orally each day for 14 days. The results of this study are shown in figure 8. The plasma total cholesterol fell from 272 mg. per 100 cc. to 247 mg. per 100 cc. after 14 days, a fall of 9 per cent ($p > 0.5$), and the total-cholesterol:phospholipid ratio fell from 1.01 to 0.85, a fall of 16 per cent ($p < 0.05$). The alpha:beta lipoprotein ratio rose from 10:90 to 14:86 (table 1).

(4) *Methyl Testosterone*

(a) *Methyl Testosterone + Ethinyl Estradiol.* Twelve men were studied for 68 weeks. Five mg. of methyl testosterone (Ciba) were administered daily sublingually for four weeks and 10 mg. for a further four weeks. During these eight weeks the men also received inert

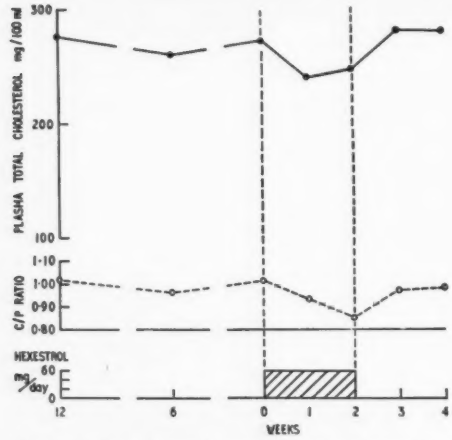

FIG. 8. The effect of hexestrol on the plasma lipids of six hypercholesterolemic men with coronary disease. Sixty mg was administered daily for 14 days.

tablets similar in size and shape to ethinyl estradiol. At the end of eight weeks tablets containing 400 μg. of ethinyl estradiol were substituted for the inert tablets, and for the next 14 weeks the men received the estrogen and 10 mg. of methyl testosterone daily; after the first two weeks 600 μg. of ethinyl estradiol were administered, and after two more weeks 800 μg. and after two further weeks 1 mg. of ethinyl estradiol was administered daily. At the end of 14 weeks combined therapy, inert linguets identical to the androgen were substituted, and the men received 1 mg. of ethinyl estradiol daily for four more weeks when identical inert tablets were again substituted for the estrogen; the men then received two groups of inert tablets for a further 12 weeks.

The results of this study are shown in figure 9. The plasma total cholesterol did not undergo any appreciable fall when ethinyl estradiol was administered in conjunction with methyl testosterone until 1 mg. of ethinyl estradiol was being received daily. When methyl testosterone was withdrawn, the plasma total cholesterol fell from a control value of 284 mg. per 100 cc. to 255 mg. per 100 cc., a fall of 21 per cent. Until 800 μg. of ethinyl estradiol was being received daily the total cholesterol-phospholipid ratio did not undergo any appreciable fall, but when methyl testosterone was withdrawn, the total-cholesterol:phospho-

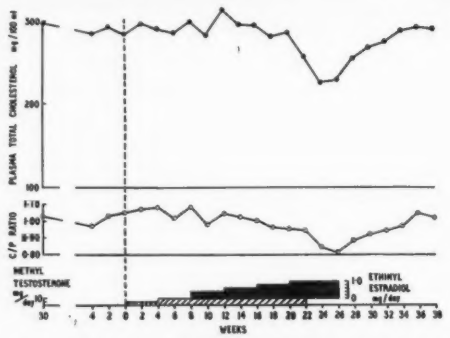

FIG. 9. The effect of the administration of methyl testosterone, and subsequently also ethinyl estradiol, on the plasma lipids of 12 hypercholesterolemic men with coronary disease.

lipid ratio fell from a control value of 1.05 to 0.81, a fall of 23 per cent.

(b) *Ethinyl Estradiol + Methyl Testosterone.* Twelve men were studied for 30 weeks. Two hundred μg. of ethinyl estradiol were administered daily for two weeks and thereafter up to the end of the tenth week the daily dose was increased by 200 μg. every two weeks. During these 10 weeks the men also received inert linguets similar in size, shape and taste to methyl testosterone linguets. At the end of 10 weeks linguets containing 20 mg. of methyl testosterone were substituted for the inert linguets, and for the next four weeks the men received the androgen and 1 mg. of ethinyl estradiol daily. At the end of four weeks of combined therapy, inert tablet, identical to

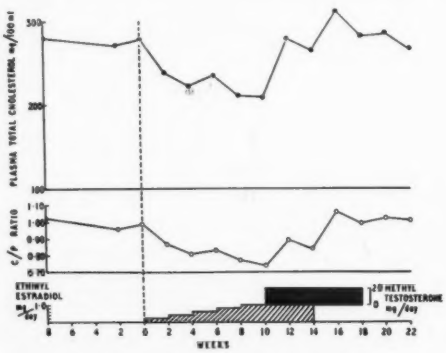

FIG. 10. The effect of the administration of ethinyl estradiol, and subsequently also methyl testosterone, on the plasma lipids of 12 hypercholesterolemic men with coronary disease.

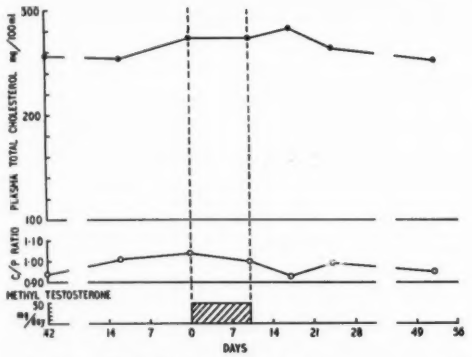

FIG. 11. The effect of methyl testosterone on the plasma lipids of six hypercholesterolemic men with coronary disease. Fifty mg. were administered sublingually each day for 10 days.

the estrogen were substituted, and the men received 20 mg. of methyl testosterone daily for four more weeks when inert linguets were again substituted for the androgen; the men then received two groups of inert tablets for a further four weeks.

The results of this study are shown in figure 10. The plasma total cholesterol fell from 278 mg. per 100 cc. to 209 mg. per 100 cc. after 10 weeks of ethinyl estradiol, a fall of 25 per cent. When methyl testosterone was administered in conjunction with ethinyl estradiol, the plasma total cholesterol rose to 279 mg. per 100 cc., and when ethinyl estradiol was withdrawn, the plasma total cholesterol rose still further to 312 mg. per 100 cc. The total-cholesterol:phospholipid ratio fell from 0.99 to 0.74 after 10 weeks of ethinyl estradiol, a fall of 25 per cent. When methyl testosterone was administered in conjunction with ethinyl estradiol, the total-cholesterol:phospholipid ratio rose to 0.89, and when ethinyl estradiol was withdrawn, the total-cholesterol:phospholipid ratio rose still further to 1.06.

The administration of methyl testosterone in these two studies did not modify or prevent any of the side effects of ethinyl estradiol, but its administration was associated with the development of clinical jaundice in four men who were consequently excluded from the study.

(c) *Methyl Testosterone.* Six men received 50 mg. linguets of methyl testosterone daily for 10 days. The results of this study are shown in figure 11. The plasma total cholesterol remained at 274 mg. per 100 cc. while methyl testosterone was being administered but rose slightly one week later to 282 mg. per 100 cc. The total-cholesterol:phospholipid ratio fell from 1.04 to 1.00 while methyl testosterone was being administered. These changes were not statistically significant. The alpha:beta lipoprotein ratio fell from 13:87 to 6:94 ($p < 0.05$) (table 1).

(5) *Progestins*

(a) *Ethinyl Testosterone + Ethinyl Estradiol.* Twelve men were studied for 26 weeks. Twenty mg. of ethinyl testosterone (anhydrohydroxyprogesterone, Ciba) were administered daily sublingually for two weeks, 40 mg. daily for two more weeks and then 60 mg. daily for the next two weeks. During these six weeks the men also received inert tablets similar in size and shape to ethinyl estradiol. At the end of six weeks tablets containing ethinyl estradiol 500 μg. daily were substituted for the inert tablets, and for the next four weeks the men received the estrogen and 60 mg. of the progesterone analogue daily; after two weeks 1 mg. of ethinyl estradiol was administered daily. At the end of four weeks of combined therapy inert linguets identical to the progesterone analogue were substituted, and the men received 1 mg. of ethinyl estradiol daily for two more weeks when identical inert tablets were again substituted for the estrogen; the men then received two groups of inert tablets for a further eight weeks.

The results of this study are shown in figure 12. The plasma total cholesterol fell from 256 mg. per 100 cc. to 225 mg. per 100 cc. after six weeks of ethinyl testosterone, a fall of 12 per cent; it fell further to 208 mg. per 100 cc. when 1 mg. of ethinyl estradiol was administered at the same time. There was a rise in plasma total cholesterol to 242 mg. per 100 cc. when ethinyl testosterone was withdrawn even although the men were still receiving 1 mg. of ethinyl estradiol daily; there was a further rise on withdrawal of ethinyl estradiol to 271 mg. per 100 cc. The total-cholesterol:phospholipid ratio did not alter appreciably after six weeks of ethinyl testosterone; it fell from the control

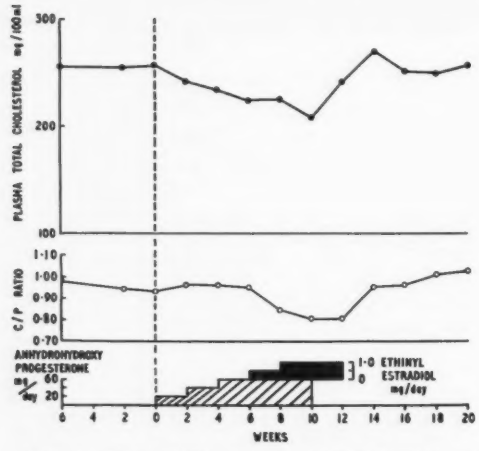

FIG. 12. The effect of the administration of anhydrohydroxy-progesterone (ethinyl testosterone), and subsequently also ethinyl estradiol, on the plasma lipids of 12 hypercholesterolemic men with coronary disease.

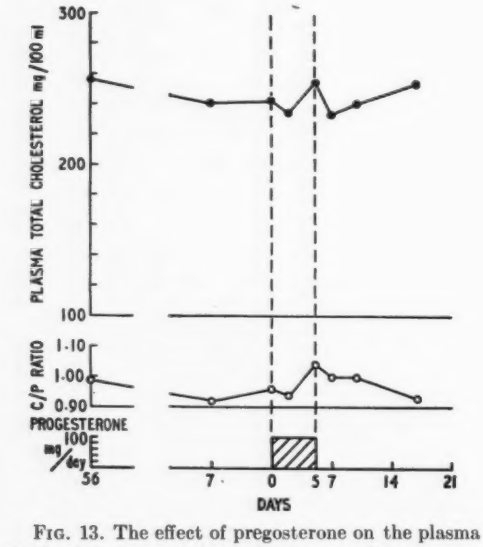

FIG. 13. The effect of pregesterone on the plasma lipids of six hypercholesterolemic men with coronary disease. One hundred mg. were administered intramuscularly each day for five days.

value of 0.93 to 0.80 when ethinyl estradiol was introduced, and subsequently rose to 1.03 following withdrawal of ethinyl estradiol.

(b) *Progesterone.* Six men received 100 mg. of progesterone (British Drug Houses) intramuscularly daily for five days. The results of this study are shown in figure 13. The plasma total cholesterol and the total-cholesterol: phospholipid ratio did not undergo any significant change during or after the course. Similarly the alpha:beta lipoprotein ratio failed to show significant change (table 1). The packed cell volumes and the weights of these men did not alter.

When the concentration of cholesterol on the alpha and beta lipoprotein fractions was expressed in mg. per 100 cc., the cholesterol on the beta lipoprotein fraction decreased absolutely and the cholesterol on the alpha lipoprotein fraction increased absolutely during the administration of ethinyl estradiol and, conversely, during the administration of methyl testosterone.

DISCUSSION

There can be no doubt from our studies on 100 survivors of myocardial infarction that ethinyl estradiol caused uniform depression of the plasma total cholesterol, the total-cholesterol:phospholipid ratio and the concentration of cholesterol attached to the beta lipoprotein fraction, and therefore a rise in the serum alpha:beta ratio. These results confirm our previous observation[12] and those of Barr, Russ and Eder,[10] Barr[11, 13] and Steiner, Payson and Kendall.[14] The percentage fall in the total-cholesterol:phospholipid ratio was greater than the percentage fall in the plasma total cholesterol whether ethinyl estradiol was administered at a low dose over a long period, in increasing doses over a moderate period or at a high dose over a short period. In these studies, ethinyl estradiol caused elevation of the plasma phospholipids as well as depression of the total cholesterol. This observation agrees with the findings of Eilert,[18] Barr and associates,[10] Barr[11, 13] and Steiner and co-workers[14] and contrasts with our previous observation that the phospholipids remained more or less constant.[12] There was no significant alteration in body weight or in plasma volume, as judged by hematocrit determinations, in these men who were not subject to any dietetic restrictions. There was no significant difference in the degree or rate of the depression of plasma total cholesterol and the total cholesterol-phospho-

ipid ratio at the end of six weeks whether ethinyl estradiol was administered at a level of 1 mg. daily, at a level of 200 μg. daily or was increased gradually from 200 μg. to 1 mg. daily. This comparative study of the dosage of ethinyl estradiol was not possible beyond six weeks as some of the men who received 1 mg. of ethinyl estradiol complained of side effects, but it suggests that a dose larger than 200 μg. daily is not more effective in depressing the circulating lipids and may even be a disadvantage as side effects are more readily encountered. Generally, the higher the plasma total cholesterol, the total-cholesterol:phospholipid ratio and the concentration of cholesterol attached to the beta lipoprotein fraction the greater the response to the administration of ethinyl estradiol.

Ethinyl estradiol was the only estrogen preparation which produced highly significant depression of the circulating lipids and of the concentration of cholesterol attached to the beta lipoprotein fraction although hexestrol and estradiol administration resulted in a similar trend. The two principal side effects of ethinyl estradiol administration, gynecomastia and depression of libido, were remarkably well tolerated and were not regarded as major obstacles to the administration of estrogens to men. However, an attempt was made to minimize these side effects by the combination of an androgen or a progestin with ethinyl estradiol.

The simultaneous administration of methyl testosterone and ethinyl estradiol resulted in partial inhibition of the depressant action of the estrogen on the circulating lipids and lipoproteins. This inhibition was apparent when ethinyl estradiol was introduced in the course of the administration of methyl testosterone and in the converse study. Moreover, continued administration of methyl testosterone following withdrawal of ethinyl estradiol resulted in further elevation of the plasma total cholesterol and the total-cholesterol:phospholipid ratio and this elevation may partly be due to the rebound sometimes seen after withdrawal of ethinyl estradiol. When methyl testosterone was given alone there was no significant elevation in the plasma total-cholesterol or the total-cholesterol:phospholipid ratio but the alpha:beta lipoprotein ratio fell significantly. The effect of methyl testosterone on the plasma total cholesterol and on the total cholesterol:phospholipid ratio was more striking when ethinyl estradiol had been administered and its action was being antagonized. These observations are in agreement with those of Barr.[11, 13] In our experience, methyl testosterone failed to ameliorate any of the side effects produced by ethinyl estradiol. The development of clinical jaundice in four men is in accord with the experiences of Werner who attributes to methyl testosterone a hepatotoxic action manifested by biliary stasis.[19, 20]

Progesterone administered intramuscularly failed to elicit any response in the circulating lipids and lipoproteins, although a progesterone analogue (ethinyl testosterone) administered sublingually produced some depression of the plasma total cholesterol and the plasma phospholipids. In our experience the administration of this progesterone analogue also failed to ameliorate any of the side effects produced by ethinyl estradiol.

The mechanism by which ethinyl estradiol ameliorates the abnormal circulating lipid and lipoprotein patterns in coronary disease is at present obscure. The liver is probably the principal site of biosynthesis and catabolism of the circulating cholesterol, the quantity of which is largely dependent on the net result of these opposing dynamic processes; either or both of these processes may be influenced directly or indirectly by ethinyl estradiol. It is important to determine whether control of the circulating lipids and lipoproteins is associated with inhibition or even regression of atherosclerotic lesions. It is encouraging that less coronary atherosclerosis has been reported in men with carcinoma of the prostate, treated with large doses of stilbestrol, compared with similar men treated with small doses or none at all.[21] Inhibition of the atherosclerotic process may not necessarily prolong life, once a myocardial infarct has occurred, and it is, therefore, essential to assess the effect of estrogens by a controlled clinical and, ultimately, pathologic study of subjects with coronary disease treated in this way.

There is considerable evidence that human coronary atherogenesis is influenced by sex. There is a striking sex difference in the incidence of the clinical manifestations of coronary sclerosis during the fourth and fifth decades. An analysis of 1000 consecutive patients with clinical coronary disease indicated that it was 19 times more common in men than in women under the age of 35 and 15 times more common under the age of 40.[27] Young men have lower alpha:beta lipoprotein ratios[5, 22-24] and a higher concentration of S_f 12–20 low density lipoproteins[25] than young women; it is probable that this sex difference in lipoprotein concentrations depends to some extent on cyclical variations which occur during the menstrual cycle and may be related to endogenous estrogen secretion.[8, 9] Morphologic studies indicate that the physical characteristics of the very masculine and robust male are just those most commonly found to excess in subjects of coronary disease.[26] The estrogenic and androgenic sex hormones seem to be mutually antagonistic so far as the circulating lipids and lipoproteins are concerned and the estrogen-androgen balance may be of considerable importance in the development of clinical coronary disease. Whether alteration of this balance by estrogens will result in retardation of the atherosclerotic process and, if so, whether belated control of this process is of any value once it has become manifest clinically, can only be determined by further investigation and assessment in terms of morbidity and mortality.

Summary

(1) The administration of ethinyl estradiol to men with myocardial infarction decreased the plasma total cholesterol, elevated the plasma phospholipids thereby depressing the total cholesterol-phospholipid ratio and decreased the concentration of cholesterol attached to the beta lipoprotein fraction.

(2) A daily dose of more than 200 μg. of ethinyl estradiol was no more effective in its influence on the circulating lipids and lipoproteins and was regarded as a disadvantage, as it was more readily associated with feminizing side effects.

(3) Hexestrol and estradiol had a similar but less marked effect.

(4) Ethinyl estradiol and methyl testosterone had a mutually antagonistic action on the circulating lipids and lipoproteins.

(5) Progesterone had no significant action on the circulating lipids and lipoproteins.

(6) Methyl testosterone and ethinyl testosterone failed to relieve the side effects of ethinyl estradiol administration.

(7) The efficacy of ethinyl estradiol administration in coronary disease must await assessment in terms of morbidity and mortality rates, rather than in its ability to correct the abnormal circulating lipid and lipoprotein concentrations.

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Summario in Interlingua

Le administration de ethinylo-estradiol a 100 superviventes de infarcimento myocardiac resultava uniformemente in le correction del anormal concentrationes de circulante lipidos e lipoproteinas. Gynecomastia e depression del libido esseva ben tolerate per le patientes sed non esseva meliorate per un preparato androgenic o un analogo de progesterona. Methylotestosterona, que effectuava un inhibition partial del effecto de estrogeno, augmentava le concentration de cholesterol del fraction lipoproteinic beta. Progesterona non habeva un effecto significative super le circulante lipidos e lipoproteinas. Le determination del effecto de ethinylo-estradiol super le atherogenese human debe depender de un evalutation a longe durantia de su influentia super morbiditate e mortalitate.

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Effect of Hypotension due to Spinal Anesthesia on Coronary Blood Flow and Myocardial Metabolism in Man

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The induction of spinal anesthesia resulted in hypotension and decreased coronary blood flow and myocardial oxygen consumption. At the same time the myocardial extraction coefficient of oxygen was not increased, indicating myocardial oxygenation to be adequate for the lower work load. This does not imply that local ischemia might not occur in the presence of coronary artery sclerosis. The coronary arteriovenous differences of glucose, lactate and pyruvate were not changed during the period of hypotension.

HIGH spinal anesthesia was used many years ago. It has been revived recently for its hypotensive effects.[1] However, some have expressed concern about the effect of the hypotension on the circulation to vital organs. Previous studies in this laboratory have dealt with the general hemodynamic effects[2] and with the cerebral[3] and hepatic[4] metabolism and blood flow. The present study employs the method of coronary sinus catheterization, devised by Goodale and associates[5] to determine the effects of arterial hypotension, due to spinal anesthesia on the coronary blood flow and oxygen and carbohydrate metabolism of the human heart.

METHODS

Twelve patients were selected at random from the medical wards. Their ages and diagnoses are listed in table 1. The general technics, including the method of premedication and catheterization of the right side of the heart, were carried out as previously described.[2] The coronary sinus was catheterized and the coronary blood flow, myocardial oxygen, glucose, lactate and pyruvate consumption were determined by methods described previously.[6, 7] The coronary vascular resistance was calculated by dividing the mean arterial blood pressure (millimeters of mercury) by the coronary blood flow (milliliters per 100 Gm. of myocardium per second). The myocardial extraction coefficient for oxygen was determined as the quotient of the coronary arteriovenous difference for oxygen divided by the arterial level (i.e., $\frac{A - V}{A} \times 100$). This term expresses the per cent of oxygen that was extracted by the myocardium from a unit of blood and has been characterized in detail in a previous report.[7]

These determinations were carried out in six of the above patients, followed by the induction of spinal anesthesia. In four of these patients the level of anesthesia was high, as indicated by a loss of tactile sensitivity to or above T-4, and by an increase in the rate of finger blood flow and pulse volume. In two patients the anesthesia level was low. In all patients, however, there was a significant fall in arterial blood pressure. A second set of determinations was done one-half hour after the spinal anesthesia had been induced. The other six patients served as double controls, without anesthesia, to determine the variations between two sets of observations one-half hour apart in the absence of hypotension. Four of the six patients given spinal anesthesia had essential hypertension (without heart failure) while all of the double controls were nonhypertensives. This was a fortuitous distribution, but as a result, the absolute values of the two groups were not strictly comparable. The main function of the double control group, however, was to indicate the *change* that occurred due to blood sampling and the manipulative procedures.

Twelve-lead electrocardiograms were taken before the study, and for seven consecutive days thereafter.

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TABLE 1.—*Clinical Data*

Patient	Age Years	Sex	Body Wt. Kg.	Clinical Diagnosis
V.L.M.	24	M	63	Anxiety neurosis
E.F.	61	M	?	Hypertension, Resolved Bronchopneumonia
M.C.	55	F	70	Hypertension
M.K.	55	M	63	Chronic Alcoholism
A.G.	58	M	64	Possible Bronchogenic Carcinoma
R.F.	62	M	51	Organic Brain Disease
B.H.	33	F	57	Alcoholic Polyneuropathy, Treated
E.T.	55	M	61	Bronchopneumonia, Resolved
J.W.	32	M	80	Secondary Lues, Treated
R.C.	55	F	78	Convulsive Disorder, Undiagnosed
P.D.	26	M	67	Bronchopneumonia, Resolved
W.F.	44	M	66	C.N.S. Disease, Unknown Type

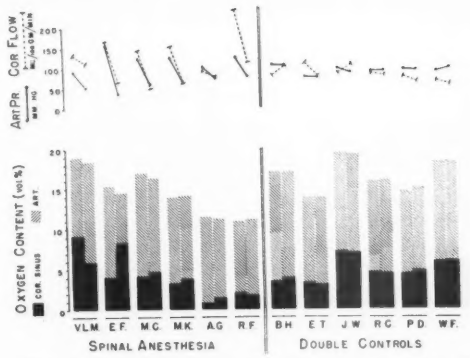

FIG. 1. Relation of coronary flow, arterial blood pressure and coronary oxygen content. In the group given spinal anesthesia, the first value for each patient is the control and the second value is the one after anesthesia was induced. The values for each patient in the "double control" group are similar except that no spinal anesthesia was given between the two determinations.

RESULTS

In all patients given spinal anesthesia the coronary blood flow fell parallel with the decrease in mean arterial blood pressure (fig. 1, table 2). The mean coronary vascular resistance thus did not change significantly, although there was much variation between individual cases. The patients in the double control series, on the other hand, showed random variations in arterial blood pressure and coronary blood flow. Despite the marked reduced coronary flow in the six patients following spinal anesthesia, four patients showed an increase in the coronary sinus oxygen content, and one (R. F.) showed only a very slight decrease. There was a decrease, therefore, in total oxygen consumption by the heart in all five. The sixth patient (V. L. M.) showed a marked reduction in coronary sinus oxygen content and a slight increase in total myocardial oxygen consumption. Since this patient, however, showed a precipitous fall in mean arterial blood pressure (from 70 mm. Hg to about 30 mm. Hg) during the course of the 10 minute sampling period, a steady state did not exist and the results cannot be included with those of other patients in the series. In 4 of the other 5 patients given spinal anesthesia, the arterial blood pressure was measured before and after the period of sampling, following induction of spinal anesthesia. This showed a slight further decrease averaging 12 mm. Hg below the level of blood pressure achieved by the anesthetic. In the final patient of this group the pressure was recorded only in the middle of the sampling period. The patients in the double control series showed only slight random variation in coronary arteriovenous oxygen differences and in total myocardial oxygen utilization.

The essential hypertension present in 4 of the 6 patients given spinal anesthesia permits a comparison between the preanesthetic values in the hypertensive and normotensive patients. The coronary flow and the left ventricular oxygen utilization appear to have been greater in the hypertensive group. Further consideration of these observations will be deferred to a future report on a larger series of patients.

Myocardial glucose, lactate and pyruvate extraction showed only slight random variation with spinal anesthesia in the three cases completely studied. The double control series showed similar slight random variation. Even these few observations indicate a distinct difference between hypotension due to spinal anesthesia, with no conclusive metabolic effect on the heart, and experimental hemorrhagic shock which produced very small or negative

TABLE 2.—*Hemodynamic Findings*

A. Before and During Spinal Anesthesia

Patient	Level of Anesth.	Mean Blood Pressure mm. Hg		Cor. Flow ml./100 Gm./min.	Cor. Res.	Oxygen			Myoc. O_2 Ext. %	Ht. Rate
		Art.	R.A.			Art. vol. %	C.S. vol. %	Util. ml./100 Gm./min.		
V.L.M.	0	93	5.8	132	42.2	19.0	9.1	13.1	52	75
	HI†	—	—	114	28.4	18.5	5.9	14.3	68	56
E.F.	0	156	2.5	165	56.6	15.3	4.1	18.5	73	79
	HI	36	1.4	68	31.8	14.5	8.3	7.6	43	48
M.C.	0	122	—	141	51.9	17.0	4.2	18.1	75	72
	HI	60	—	50	72.4	16.3	4.7	5.8	71	40
M.K.	0	123	3.8	152	48.5	13.9	3.3	16.1	76	71
	HI	63	—	60	63.0	14.0	3.7	6.2	74	73
A.G.	0	100	3.9	91	66.3	11.5	0.7	9.9	94	100
	LO	73	0.9	76	57.5	11.3	1.5	7.5	87	100
R.F.	0	123	2.5	238	30.9	10.9	2.1	20.9	81	71
	LO	78	−.5	114	41.1	11.1	1.8	10.6	84	75
Mean ±σm		119.5 ±9.9	3.7	153.2 ±21.7	49.4 ±5.4	14.6 ±1.4	3.9 ±1.3	16.1 ±1.8	75.2 ±6.1	78.0 ±5.0
		62.0* ±8.2	.6	73.6* ±12.3	53.2 ±8.3	13.4 ±1.1	4.0 ±1.4	7.5* ±.9	71.8 ±8.7	67.2 ±12.0

B. Double Control Series

B.H.	0	105	5.2	80	78.9	17.0	3.5	10.8	79	87
	0	105	5.1	104	60.7	17.0	3.9	13.6	77	88
J.W.	0	95	—	85	66.9	19.4	7.1	10.5	63	62
	0	85	—	101	68.0	19.2	7.0	12.3	64	65
E.T.	0	73	3.2	108	40.6	13.9	3.3	11.5	76	73
	0	73	1.8	75	58.4	13.9	3.1	8.1	78	67
R.C.	0	88	—	83	63.7	15.8	4.5	9.4	72	75
	0	89	—	79	67.9	15.9	4.4	8.9	72	65
P.D.	0	91	7.8	73	75.3	14.5	4.4	7.4	70	51
	0	90	8.6	63	85.7	14.9	4.7	6.4	68	45
W.F.	0	88	—	62	85.4	18.2	5.8	7.7	68	73
	0	95	—	56	102.0	18.2	5.9	6.9	68	64
Mean ±σm		90 ±4.7	5.4	81.8 ±6.8	68.5 ±7.1	16.5 ±1.0	4.8 ±.6	9.6 ±.8	71.3 ±2.5	70.2 ±5.5
		89.5 ±4.7	5.2	79.7 ±8.7	73.8 ±7.5	16.5 ±.9	4.8 ±.6	9.4 ±1.3	71.2 ±2.5	65.7 ±6.1

Art. = arterial; C.S. = coronary sinus; Myoc. O_2 Ext. = myocardial coefficient of extraction of oxygen, (i.e., A − V/A); σm = standard error of mean; Util. = left ventricular utilization; R.A. = right atrium.

* indicates a statistically significant change from initial control value with $p \leq .01$.

† Not included in mean values due to marked drop in blood pressure during sampling period.

myocardial pyruvate extraction, together with high arterial concentrations of lactate, glucose and pyruvate.[8]

In no instance were electrocardiographic changes suggestive of myocardial hypoxia observed, except for patient V. L. M. In this case there was evidence of subendocardial ischemia that followed a sudden blood pressure drop, with reversion to normal in less than 24 hours.

TABLE 3.—*Metabolic Findings*

A. Before and During Spinal Anesthesia

Patient	Level of Anesth.	Glucose				Lactate				Pyruvate			
		Art. mg. %	A-V mg. %	Util. mg./100 Gm./ min.	Ext. %	Art mg. %	A-V mg. %	Util. mg./100 Gm./ min.	Ext. %	Art. mg. %	A-V mg. %	Util. mg./100 Gm./ min.	Ext. %
V.L.M.	0	84.0	2.1	2.8	2.5	3.8	1.1	1.5	29.0	1.28	.46	.61	36.0
	HI	—	—	—	—	—	—	—	—	—	—	—	—
M.C.	0	117.7	3.1	4.4	2.6	12.2	5.5	7.8	45.1	2.02	.91	1.28	45.1
	HI	111.6	−2.5	−1.3	−2.2	13.7	4.8	2.4	35.0	2.29	.93	.47	40.6
M.K.	0	68.3	1.3	2.0	1.9	14.3	4.0	6.1	30.8	2.38	1.12	1.83	47.8
	HI	76.3	3.8	2.3	6.7	21.6	3.6	2.2	16.7	—	—	—	—
A.G.	0	56.6	0	0	0	6.8	1.7	1.5	25.0	1.36	.59	.54	43.4
	LO	56.8	2.3	1.8	4.1	8.3	2.5	1.9	30.2	1.71	.69	.52	40.3
Mean		81.7	1.6	2.3	1.8	9.3	3.1	4.2	32.5	1.76	.77	1.07	43.1
		81.6	1.2	0.9	2.9	14.5	3.6	2.2	27.3	2.00	.81	.50	40.5

B. Double Control Series

B.H.	0	86.0	3.8	3.0	4.4	4.8	2.5	2.0	52.1	2.42	1.72	1.37	71.1
	0	84.3	—	—	—	4.8	4.1	4.3	85.4	2.07	.12	.13	5.8
E.T.	0	73.9	1.0	1.1	1.4	4.7	1.0	1.1	21.3	1.25	.26	.28	20.8
	0	79.0	−.7	−.5	−.9	4.7	.8	.6	17.0	1.26	.27	.20	20.4
J.W.	0	88.2	6.2	5.3	7.0	4.8	2.2	1.9	45.8	1.19	.23	.20	19.3
	0	91.0	3.3	3.3	3.6	5.7	3.0	3.0	52.6	1.20	.23	.23	19.2
R.C.	0	80.3	9.5	7.9	11.8	8.0	3.9	3.2	48.8	1.68	.97	.80	57.7
	0	78.4	9.4	7.4	12.0	7.6	3.6	2.8	47.4	1.62	.96	.76	59.2
P.D.	0	54.3	−6.4	−4.7	−11.8	7.7	3.6	2.6	46.8	2.03	1.15	.84	56.7
	0	63.2	.1	.1	.2	7.4	3.6	2.3	48.8	1.87	.57	.36	30.5
Mean		76.5	2.8	2.5	2.6	6.0	2.6	2.2	43.0	1.71	.87	.70	45.1
		79.2	3.0	2.6	3.7	6.0	3.0	2.6	50.2	1.60	.43	.34	27.0

For abbreviations see table 2; A − V = coronary arteriovenous difference; Ext. = coefficient of extraction (A − V/A).

DISCUSSION

Arterial hypotension has been feared as a potential hazard to the human heart during spinal anesthesia. Any deleterious effects should depend upon a possible undue restriction of coronary blood flow by the hypotension, out of proportion to any decrease in myocardial oxygen demand at the diminished level of cardiac work.

Studies in dogs have demonstrated the direct relation of the coronary blood flow to the arterial blood pressure[9] and to the oxygen demands of the heart.[10] The present studies in man also show a direct relation between arterial blood pressure and coronary flow. It has been previously demonstrated[2] that the cardiac output also decreases under the same hypotensive conditions. The work load on the heart is thus decreased. At the same time, the myocardial oxygen extraction coefficient $\left(\frac{A - V}{A}\right)$ is not increased, but in some instances is actually decreased. When the oxygen supply to the myocardium is deliberately restricted, the myocardial oxygen extraction coefficient is greatly increased.[11] These findings indicate that there is an adequate myocardial oxygen supply relative to work demand during the hypotension of spinal anesthesia, despite the reduced coronary flow.

An alarming exception to this favorable situation during spinal anesthesia was noted

in patient V. L. M. Peripheral vascular collapse and subendocardial ischemia were precipitated by removing 70 ml. of blood for the postspinal observations, compared with only a slight fall in blood pressure and normal electrocardiograms in the other patients during a comparable blood sampling period. Evidently the high spinal anesthesia in this one case had expanded vascular volume to a point where any further reduction of effective blood volume critically limited venous return to the heart. In addition, the preganglionic sympathetic blockade may have been complete enough to block any effective neurogenic vasoconstrictor response. Only in this patient was there a marked increase in myocardial oxygen extraction $\left(\frac{A - V}{A}\right)$, with transient electrocardiographic changes confirming the presence of myocardial hypoxia. This combination of high spinal anesthesia and mild blood loss could account for some of the more serious sudden hypotensive responses seen during surgery.

Despite the decreased cardiac work, we were unable to demonstrate altered coronary arteriovenous differences of glucose, lactate or pyruvate. This is in agreement with our previous findings[7] that the extraction of these substances by the myocardium is related primarily to their own arterial levels and not to changes in coronary blood flow or cardiac work. The present acute experiments would, therefore, indicate that an essential determinant of coronary flow is the oxygen demand rather than the immediate need for carbohydrate substrate. It is not surprising that this is so, since the heart has reserves of glycogen from which to draw, in addition to alternate fat and protein substrates.

Hemorrhagic shock in dogs[8] presents a striking contrast to the hypotension of spinal anesthesia. In both groups, the blood pressure is reduced to a comparable level. The patients under spinal anesthesia, however, are not in a state of shock similar to that of dogs in hemorrhagic shock. They do not have signs of adrenalin release such as tachycardia and high arterial glucose, lactate and pyruvate levels, which are found in dogs after shock from hemorrhage. Furthermore, they do not show the abnormal pattern of myocardial carbohydrate metabolism that occurs during shock. The hypotensive patients show a reduction in coronary flow and left ventricular oxygen consumption which is proportional to the decreased work load. The dogs in shock, on the other hand, maintain coronary flow and left ventricular oxygen consumption with a resulting decrease in mechanical efficiency. The myocardial oxygen extraction coefficient is unchanged or decreased in the spinal hypotensive patients, indicating adequate myocardial oxygenation. In the dogs in hemorrhagic shock, however, the oxygen extraction coefficient is significantly increased, suggesting relative coronary insufficiency.

These findings partly answer the query of Dripps and Vandam[12] concerning the adequacy of the coronary flow during spinal anesthesia. It should be emphasized, however, that coronary artery sclerosis could obviously lead to regional myocardial ischemia in the face of a decreased perfusion pressure. Furthermore, even a small blood loss during spinal anesthesia can produce circulatory collapse, unless promptly controlled by replacement or pressor agents.

Summary

The coronary blood flow and myocardial oxygen consumption decreased during the period of hypotension caused by spinal anesthesia in man. At the same time, the myocardial oxygen extraction coefficient was not increased, indicating that myocardial oxygenation was adequate for the lower work load. This does not imply that local ischemia might not occur in the presence of coronary artery sclerosis. The coronary arteriovenous differences of glucose, lactate and pyruvate were unchanged during the period of hypotension.

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SUMMARIO IN INTERLINGUA

Le fluxo coronari de sanguine e le consumption myocardial de oxygeno se abassava in humanos durante le periodo de hypotension causate per anesthesia spinal. Al mesme tempore le coefficiente del extraction myocardial de oxygeno non esseva augmentate. Isto indica que le oxygenation myocardial esseva adequate pro le reducite carga de labor. Il non seque que ischemia local es impossibile in le presentia de sclerosis del arteria coronari. Le arterio-venose differentias coronari in glucosa, lactato, e pyruvato monstrava nulle alteration durante le periodo hypotensive.

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CLINICAL CONFERENCE

EDITOR: EDGAR V. ALLEN, M.D.
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The Treatment of Hypertension with Modern Drugs

By HENRY A. SCHROEDER, M.D. AND H. MITCHELL PERRY, JR., M.D.

DR. SCHROEDER: Most of us have been confused by the varying and conflicting reports in the literature and at meetings concerning the effectiveness or ineffectiveness of modern antihypertensive drugs and their place in the treatment of arterial hypertension. During the past five years we have been given a number of agents which appear to counteract to varying degrees the general vasospasm with which hypertension is associated, but all of which have produced toxic side effects or serious manifestations of their primary actions. The purpose of this conference is to attempt a clarification of the present situation in regard to such agents and similar ones being developed, and to consider when they should and should not be used. Perhaps it would be well to begin with a short resumé of the pharmacology of the more important of them. Dr. Perry, you might discuss the *Rauwolfia* alkaloids, protoveratrine and its relatives, ganglionic blocking agents and hydralazine. That order, progressing from a central encephalic locus of action to a peripheral one at the vascular smooth muscle, is a good one. Let us confine ourselves to pure compounds.

DR. PERRY: The first three act primarily upon autonomic nerves. Reserpine, an alkaloid in the whole root of *Rauwolfia serpentina*, is a slowly acting corticohypothalamic depressant which produces partial nervous sympatholysis by inhibiting impulses to the sympathetic center. The extreme flatness of the dosage-response curve and the relatively weak action obviate the hypotensive episodes which complicate the use of other more potent vasoactive drugs. Unpleasant side effects include nasal obstruction, diarrhea, obesity, anxiety, nightmares and insomnia. Activation of peptic ulcers and colitis has been seen. Of much greater import, however, is an occasional extreme psychotic depression with suicidal tendencies. The limited antihypertensive effect may partially explain the failure to observe tolerance.

Veratrum alkaloids, of which protoveratrine is a purified principle, influence vasomotor centers in the medulla via the vagal and the carotid bifurcation receptors resulting in parasympathetic overactivity. They appear to stimulate the depressor nerves, thus causing a fall in blood pressure. The small margin of safety between therapeutic and toxic amounts makes dosage critical. The side effects are bradycardia, hypotension, nausea and vomiting. The rapid appearance of tolerance limits the ability of these agents to maintain continuous normotension.

Ganglionic blocking agents, of which hexamethonium and pentolinium salts are examples, diminish all nervous transmission at the autonomic ganglia. Their potency may initially produce acute hypotensive episodes which respond to a supine position. In general, the beneficial effects are those of sympatholysis, while the undesirable effects are those of parasympatholysis and include failure of visual accommodation, dry-mouth, constipation and difficulty with urination. The considerable tolerance, which is the rule when these agents are used alone, can be largely suppressed by combination with hydralazine. Apparently after a period of months, the effective dose becomes stabilized, even without the addition of an extra drug. They are quite rapidly ex-

creted and therefore must be given at regular intervals in order to maintain minimal variation in blood levels.

A PHYSICIAN: If your purpose is to block the sympathetic portion of the autonomic nervous system and many of the undesirable side effects result from tampering with the parasympathetic portion, why do you not use true sympatholytic agents?

DR. PERRY: Unfortunately with the known sympatholytic compounds, a dose, sufficient to produce an adequate hypotensive effect, is intolerable for any extended period, primarily because of tachycardia. Sufficiently potent new ones may be found which might replace the blocking agents.

Let us return to the pharmacology of hydralazine which is an extremely reactive chemical and a most valuable agent. Only a weak sympatholytic action can be demonstrated. It is quite rapidly altered in the body and probably undergoes more than one reaction. In vivo, hydralazine apparently binds sulfhydryl compounds since the combination can be isolated from the urine. In vitro, therapeutic levels of this drug combine with physiologic concentrations of pyruvate and other carbonyl reagents. Experimentally, it acts on *constricted* vascular smooth muscle. It is a true renal vasodilator; with its relatives, it has the unique property of increasing blood flow in the face of a lowered blood pressure. Isolated coronary arteries are also dilated. Our current ideas on its probable mode of action, however, involve the metal binding capacity of hydralazine, since it seems to have only this property in common with a group of non-neurogenic antihypertensive agents, such as azide, nitroprusside and thiocyanate. Since it can act as an antienzyme, perhaps an enzymatic reaction rate is altered by interference with metallic coenzymes, resulting in a changed irritability of vascular smooth muscle.

A PHYSICIAN: Do the other hydrazides, particularly the antituberculous agents, isoniazid and iproniazid, have similar metal binding powers and antienzyme activities?

DR. PERRY: They do. The relative strengths of their chelating capacities for the various transition metals is somewhat different for each compound. The antienzyme action of each also differs and may be quite specific.

There is no good evidence that the usually unequivocal but seldom dramatic antihypertensive effect of hydralazine is mediated via the central nervous system, although a central action has been demonstrated. It is a prolonged dilator, even on isolated vascular beds. Its antihistaminase activity, which may or may not involve a metal, partially explains some of the side effects, particularly, nasal obstruction and headache. In addition, tachycardia, anorexia, nausea and vomiting may occur. Tolerance is common when it is used alone, but seldom appears when a nerve-acting drug is added.

A PHYSICIAN: Sir John Parkinson recently quoted Sir Robert Hutchison as praying that we might be delivered "from inability to let well enough alone, from too much zeal for the new and contempt for what is old, . . . and from making the cure more grievous than the ill." How does this apply to the use of these potent agents whose distressing side effects you have just enumerated?

DR. PERRY: In effect, you would like to know the chance of helping the patient, the danger of hurting him, in either case, how uncomfortable are you going to make him for how long and, finally, whether there isn't a better way to do the same job. The new antihypertensive agents have been used in many ways by different investigators with varying results. Our experience in severe stages of the disease has been confined largely to an oral combination of hydralazine and methonium compounds. Those who wax enthusiastic about drug therapy claim that all elevated blood pressure can be reduced to normalcy with sufficient cooperation, perseverance and medication. Iconoclasts are skeptical both of such generalizations and of the value of whatever normotension is achieved. Beneficial effects of lowering blood pressure can be definitely established only for the small group of patients in the "malignant" phase of hypertension, as characterized by a mean diastolic pressure in excess of 130 mm. Hg, severe renal dysfunction and exudative and hemorrhagic retinitis with edema of the optic discs. Untreated, this syndrome is rapidly pro-

gressive and almost always fatal within a year or two; whereas any treatment resulting in normotension and uncomplicated by increasing renal failure usually prolongs life and may restore the capacity to work. For the much larger group of patients with less severe degrees of hypertension, the statistical evidence, necessary indisputably to prove the value of treatment, is not yet available. Hypertension, however, is associated with a high incidence of vascular accidents, and our experience suggests that lowering the intra-arterial pressure diminishes such episodes in patients who have previously experienced one or more attacks.

As to the chance of harming the patient with drug therapy, it is very small if minimal precautions are observed. We have recognized no irreversible reaction to the drugs in the last 36 months and the rare prior cases occurred when control was poor and conditions of treatment not ideal. Hence we feel that permanent harm will not come to anyone who continues to take drugs under supervision. Discontinuation, on the other hand, may result in a rebound hypertension followed by vascular accident or progressive renal failure.

A comparison of the advantages and disadvantages of lowering an elevated blood pressure, per se, suggests that the value almost always outweighs the risk, since both increase proportionately to the severity of the disease. Undesired side effects, which plague all forms of treatment, increase the danger only slightly. With a combination of hydralazine and methonium therapy carefully administered, the overall hazard is small. Initially, drug-induced hypotension is not rare. Although alarming, this clinical picture must be sharply differentiated from shock, by the presence of peripheral vasodilatation and normal cardiac rate. In our experience, such episodes are transient; moreover, there has been no accompanying evidence of myocardial anoxia, and the syncope which accompanies cerebral ischemia responds readily to the supine position. No permanent damage, resulting from clot formation or oxygen deficit, has been observed by us in well treated patients. Drug-induced parasympatholysis may lead to obstruction of hollow viscera. Parasympathomimetic drugs, catheterization or even prostatectomy may be needed to control urinary retention in the male with prostatism. We have never seen paralytic ileus result from methonium therapy. With laxatives, an intelligent, cooperative individual can control his bowels, which pose the most stubborn and persistent problem. In particularly recalcitrant cases, gastrointestinal exposure to the autonomic blocking agent can be reduced by parenteral administration. The combination of constipation and renal decompensation leads to increased methonium absorption and decreased excretion, a condition which is self-perpetuating, since an accumulation of drug further reduces both gastrointestinal motility and glomerular filtration pressure. We treat the side effects as they appear.

Temporary discomfort can be expected after any considerable alteration in hemodynamics. For weeks or months after the initiation of drug therapy, considerable inconvenience is inevitable. The altered hemodynamics and the depressed nervous transmission are particularly marked for patients with severe stages of hypertension. Their blood pressures are very high and large doses of blocking agents are required. They, therefore, have all the symptoms of parasympatholysis plus anorexia and mental depression added to their woes. This would indeed be a high price to pay indefinitely for normotension, but fortunately the unpleasant side effects diminish and, except for masculine impotence, all finally vanish, although their complete disappearance usually takes many months.

A better way than this involved, sometimes unpleasant, and inconvenient method for the control of hypertension is needed, but none has yet been devised which consistently affects the severe stages of the disease. In reality, such therapy is no more complicated, inconvenient or dangerous than is the treatment of severe diabetes.

DR. SCHROEDER: Actually, the greatest dangers to life which we have encountered have involved cessation of therapy in severe and malignant stages. Forty per cent of patients in the former and all in the latter stages have died of the complications of hypertension, when therapy was stopped. These figures,

compared to total mortality rates of under 4 per cent for severe benign and 14 per cent for malignant stages treated adequately, enforce the implication that therapy, once begun, should be continued.

A PHYSICIAN: How do you feel about surgical sympathectomy of the Smithwick or Grimson types?

DR. PERRY: Adequate surgical sympathectomy unquestionably prolongs life when it lowers blood pressure, but it fails to relieve hypertension permanently in a majority of cases. For severely hypertensive patients who will not or cannot tolerate a satisfactory medical regimen, it is usually the only recourse. Sometimes its efficacy, like that of chemical sympathectomy, can be enhanced by hydralazine or restriction of dietary salt.

A PHYSICIAN: What about total adrenalectomy?

DR. SCHROEDER: To my knowledge, no one has yet been able to prove adrenal cortical overactivity in the majority of hypertensive patients. Certain persons appear to show its signs; in them, removal of the offending organ or suppression of its activity by specific antimetabolites is logical. When we can measure the overactivity chemically or functionally as we do in hyperthyroid states, we can then proceed logically and confidently. To remove an organ which is not directly involved in a disease process is hardly a fair therapeutic measure and may produce an equally bad, though different, disease. Of course, hypertension can be induced in animals by certain steroids and salt, but it does not follow that all hypertension in human beings is caused by steroids and salt. Similarly, despite the pandemic of experimental renal hypertension in laboratory animals, it does not follow that all human hypertension begins on a renal basis. The universality of human moderator-nerve hypertension is equally unproven. Human counterparts of each of these types of high blood pressure do exist, however, and it is likely that more than one influence–eurogenic, renal or adrenal–is operative in severe cases. Our diagnostic methods are not good enough yet to separate such influences. High blood pressure is only a sign caused by a variety of conditions and is not a disease in itself.

A PHYSICIAN: What is the right time to start treating hypertension?

DR. SCHROEDER: This is a difficult question to answer because the disease itself produces serious secondary pathologic changes at widely varying rates in at least three different organs. Increased intra-arterial pressure, sustained for many months or years, leads to cardiac hypertrophy and may progress to dilatation and failure; it leads to arteriolar nephrosclerosis which may terminate in diminished renal function and eventual uremia; and, most important, it apparently leads to an increased rate of progression of atherosclerosis. The eventual results are cerebral vascular accident, either hemorrhage or thrombosis, coronary arterial occlusion and other less common arterial accidents.

Obviously the right time to treat any patient is before irreversible damage is done. After damage has appeared it is still the right time to treat, in hope of preventing further pathology. Ideally, all patients should be treated when the blood pressure first becomes and remains elevated without symptoms or signs of secondary pathologic changes. An ounce of prevention is still worth a pound of cure. Unfortunately, modern drugs carry a certain risk of disability. They may produce side effects which are annoying to an asymptomatic individual; they may result in serious new diseases or, rarely, cardiovascular accidents for which the stage has already been set. The task facing any physician, therefore, is to weigh the risks of the disease against the hazards of therapy.

It is our practice at the present time to bring the blood pressure to normal by drugs, even in early stages of hypertension, realizing full well that late side effects or toxic reactions, now undisclosed, may become manifest in a few years. We watch patients carefully for such occurrences and any new and strange symptom is initially attributed to the drugs. We believe that treatment is mandatory when the "malignant" or accelerated stage of hypertension is present as previously defined. We believe that treatment is essential for prolongation of life

when a patient has had one cerebral accident or congestive heart failure. In all other patients, treatment is elective, although in many it should be strongly urged. While it is true that a certain minor percentage of older individuals live to a ripe old age with sustained chronic hypertension, no one is able to predict the occurrence of cerebral vascular accident, heart failure or coronary occlusion. When it becomes possible to pick out those who will not have such accidents and in whom hypertension does not appear to be doing damage, they obviously should not receive treatment. Despite the statement that all patients with diastolic hypertension should be treated practically, they all cannot be at the present time.

A PHYSICIAN: What drugs do you use to treat hypertension?

DR. PERRY: Considerable controversy continues about which drugs are the most effective and least distressing. In general, the more effective the agent, the more serious are the side effects. Ordinarily, we use one, two or three agents depending on the severity of the hypertension. If psychotic depression or agitation is not produced, reserpine benefits most patients. Although its hypotensive effect is usually slight for those whose blood pressure is labile and rarely elevated (except in a physician's office), it is often sufficient to sustain normotension. The amount taken is not critical since a wide range of doses is effective without being toxic. For those with more severe hypertension and a normal blood pressure only during sleep, induced by heavy sedation, it is necessary to add hydralazine to achieve normotension. A hypotensive effect is usually obtained but is seldom abrupt; hence, the intake does not have to be finely adjusted. Relatively small quantities of the order of 250 mg. per day are used, since they generally suffice and since they obviate most of the delayed reactions. To lower fixedly elevated diastolic pressures, a ganglionic blocking agent is added to hydralazine and reserpine in a dose adequate to produce the desired result. The action of this drug is sufficiently dramatic that dosage must be carefully regulated. To minimize the wide fluctuations in blood pressure and also to prevent the very frequent tolerance to methonium compounds, it is often necessary to increase the hydralazine intake. Reserpine may lessene th required dosage of other drugs, even if alone it does not cause a significant change in blood pressure, and it frequently helps to correct methonium constipation. Perhaps the following case will indicate the method of therapy and the result achieved in severe hypertension:

L. L., a white male, was 34 years old when he was first seen in November, 1951 because of headaches for three months. At that time fundoscopic examination revealed hemorrhages and exudates without papilledema. His blood pressure was 250/140 mm. Hg and his heart was enlarged, although his lungs were clear and there was no pedal edema. He excreted only 5 per cent of intravenously injected phenol red within 30 minutes, and 2 plus albuminuria was present, without nitrogen retention. Hexamethonium chloride every four hours by mouth was begun in increasing amounts until his supine blood pressure, which had not changed with hospital rest, fell to an average of 180/110 mm. Hg,* with occasional readings of 140/90 mm. At that time, the size of his hexamethonium dosage was made contingent on the level of his blood pressure. Oral hydralazine was then added and the fluctuations of blood pressure became smaller. He was maintained normotensive by 0.15 Gm. hydralazine, five times a day, with a simultaneous variable intake of hexamethonium chloride as follows: 1 Gm. for any sitting systolic pressure over 140 mm. Hg, 0.50 Gm. for pressures between 130 and 140 mm. and 0.25 Gm. for pressures between 120 and 130 mm. He was then given a sphygmomanometer and taught to use it. After three weeks in the hospital, he returned to work immediately, although constipation, dry-mouth and some amblyopia persisted. Within two months he was free of symptoms. He has since continued his work as farmer and truck driver. About four years after beginning therapy, he is taking 0.10 Gm. of hydralazine and an average of 0.12 Gm. of hexamethonium chloride, five times a day, to maintain an average sitting blood pressure of 150/92 mm. Hg. Although there are no visible lesions in his ocular fundi and his excretion of intravenously injected phenol red has increased to 12.5 per cent in 15 minutes, his albuminuria persists.

A PHYSICIAN: Do you have any opinions on the relative merits of reserpine or protoveratrine as compared with the whole root of *Rauwolfia serpentina* or veratrum viride? Do you advocate combinations of drugs in the same pill?

* In this and subsequent mean levels of blood pressure, given in case reports, either 35 or 150 successive readings were averaged.

DR. SCHROEDER: We have no strong opinions on the first question. The whole root of *Rauwolfia serpentina*, however, contains 14 alkaloids, among them yohimbine which is classed as a renal irritant and is said to be contraindicated in kidney disease. I know of no studies bearing on renal irritation due to the whole root, but I prefer not to use it extensively until absence of irritation has been shown. Pure compounds are usually better to use in the long run than are mixtures, if the effects desired are produced as well as by the crude material. Protoveratrine, properly administered, can be a very useful drug in those patients unable to take ganglionic blocking agents. By combining effective hypotensive doses with hydralazine, relatively even control of blood pressure is often seen, impossible to achieve with either drug alone. Apparently, the mixture of protoveratrine A and B represents the active hypotensive (and emetic) principle of cruder preparations. A study made in our clinic several years ago by Gropper, Surtshin and Hedrick on a partly purified material was disappointing.

In answer to the second question, we never use combinations of drugs in one pill. The practice of combining two drugs with different actions is illogical. The dose of one may be constant and that of the other, variable. Reserpine requires a constant dosage which must usually be reduced in time. The ganglionic blocking agents need variable doses. Protoveratrine needs a dose different in the morning from later in the day. Hydralazine is usually constant but varies from patient to patient. Putting any two into one pill would require large numbers of different combinations with varying strengths of each. Nor do we advocate the "baked Alaska" pill, in which two counteracting drugs, such as a stimulant and a depressant, are combined. These supposedly convenient aids assume that all men and their dysfunctions are alike.

A PHYSICIAN: In what percentage of patients does hypertension persist despite drug therapy?

DR. PERRY: In our experience, no patient has initially proved totally resistant to combined hydralazine and methonium compounds. In fact, the blood pressure of any untreated cooperative patient can be brought down to normal with the adequate use of drugs and maintained there indefinitely, if it seems desirable. Sometimes the dosages required are very large. Of course, in the presence of sufficient renal damage, one must be satisfied with merely moderating the hypertension, since normotension is incompatible with adequate glomerular filtration and therefore with life. Occasionally considerable tolerance occurs in patients who have begun therapy and then discontinued it. Such patients require much larger quantities of drugs for control each time treatment is reinstituted. The following case is the most striking example of this phenomenon that we have observed and represents the only instance when we were unable to affect human hypertension by a combination of oral hydralazine and autonomic blocking agent. It also illustrates the good results that can be achieved in the face of azotemia and the dramatic disappearance of cardiac failure as an elevated blood pressure is lowered.

J. M., a Negro man, was 39 years old when he was first seen in December, 1953. His obvious dyspnea had gradually increased during the previous year. His blood pressure was 246/148 mm. Hg. Hemorrhages, exudates and papilledema were evident in both ocular fundi. Examination of his chest revealed basal rales and marked cardiomegaly. Azotemia was not present and the excretion of intravenously injected phenol red was 18 per cent in 15 minutes, but there was 4 plus albuminuria. Since hospital rest failed to alter the hypertension significantly, oral administration of hexamethonium chloride was begun. Within 72 hours his blood pressure fell to 150/90 mm. Hg and, simultaneously, the rales in his chest disappeared. Although his intake of drug was only 1 Gm. per day, he refused further therapy because of nausea, distention and asthenia.

Six months later, he was readmitted to the hospital after digitalization failed to control severe respiratory distress, anasarca, and oliguria. To his previous abnormal physical findings, which had persisted essentially unchanged, were added bilateral pleural effusions, a diastolic gallop rhythm, hepatomegaly, ascites and bilateral pedal edema. The formerly normal nonprotein-nitrogen level had risen to 71 mg. per 100 ml. of blood. He now agreed to oral pentolinium therapy. The dose was gradually increased to an average of 2.5 Gm. per day in divided doses before his blood pressure fell to normal levels again. With normotension, heart failure quickly vanished. To allow adequate renal filtration, his blood pressure was maintained at a

compromise level of 170/110 mm. Hg. The nonprotein-nitrogen value immediately before discharge from the hospital had decreased to a normal 27 mg. per 100 ml. of blood and he was sent home with an average daily dose of 1 Gm. each of oral hydralazine and pentolinium tartrate.

For four months he took approximately this amount of medication regularly and then was able to return to work; his mean sitting systolic pressure was 155 mm. Hg. Feeling that he was cured, he then discontinued treatment. His final readmission was 43 days later. Again he was in marked respiratory distress. His blood pressure was 200/140 mm. Hg. Fundoscopic examination revealed blurred optic discs without frank papilledema, but there were fresh hemorrhages and exudates. The signs of cardiac failure were more marked than on previous hospital entries. The nonprotein-nitrogen level was 105 mg. per 100 ml. of blood. An attempt was made to recontrol his blood pressure with hydralazine and pentolinium tartrate by giving increasing parenteral doses. After 4 Gm. of pentolinium tartrate and 2 Gm. of hydralazine within a 24 hour interval had no significant effect, he was given 0.5 Gm. of each intravenously in the same syringe during a period of three minutes. The resultant fall in diastolic pressure from 145 to 130 mm. Hg lasted only for seven minutes. Thereafter his uremia rapidly progressed and he died of renal failure two weeks after hospitalization.

DR. SCHROEDER: One sees reports in which patients were alternatively given placebos and these drugs. The usual result of such studies has been to indicate that the drugs are relatively ineffective. We have noticed the same phenomenon ourselves when the drugs were discontinued or when placebos were used. I know of no better way to produce tolerance than to give these agents intermittently. It is essential to therapy to apply even continuous therapeutic pressure, increasing to the point where the desired results are achieved without intermittency or periods of discontinuation. This phenomenon is not at all understood but it may be likened in a broader sense to that of bacterial resistance to chemotherapeutic agents used intermittently in an infection. There appears to be something about normotension, when achieved with these drugs, which carries with it a favorable outcome insofar as the continued action of the drugs themselves is concerned. Two, three or even many times the original dose may become necessary when patients are taken off and put back on. One of the most prevalent factors in producing this curious kind of tolerance to the agents lies in the insecurity of the physician when he first sees the blood pressure falling to normal levels from very high ones and the patient has symptoms associated with this fall. He then becomes worried and discontinues the drug; the blood pressure soon returns to its previous levels and he finds it extremely difficult to control the hypertension from then on. On the other hand, we have not observed tolerance developing when these drugs were properly used and normotension or a reasonable facsimile thereof was achieved for long periods of time in a fresh, untreated case.

DR. PERRY: In fact, we have observed quite the reverse. Eventually, there is a significant diminution in the quantities of hydralazine and methonium compounds needed to maintain a normal blood pressure. For instance at the end of the first year of treatment, 79 unselected patients who had maintained diastolic pressures below 100 mm. Hg with these two drugs alone took only 73 per cent of their initial doses of blocking agent; at the end of two and three years the required percentages were 57 and 46, respectively. The diminution in hydralazine intake was only slightly less. A few have been able to discontinue drugs entirely, while some are controlled with reserpine alone and some with a combination of reserpine and hydralazine. In striking contrast, patients whose diastolic pressures consistently exceeded 100 mm. Hg for one reason or another continued to use approximately their original doses of both agents to maintain even their inadequate blood pressure control. The following case illustrates the steadily decreasing amounts of antihypertensive agents needed to produce successively longer and more complete remissions of hypertension.

A. R., a white woman, was 34 years old at the time she first entered Barnes Hospital in October, 1951 with a 12-year history of an infected kidney. Physical examination was not remarkable except for a few hemorrhages without exudates or papilledema in the ocular fundi, a blood pressure of 240/120 mm. Hg, and cardiomegaly. There was no albuminuria; the excretion of intravenously in-

jected phenol red was 25 per cent in 15 minutes; but intravenous pyelography suggested right pyelonephritis. With a daily 0.5 Gm. hydralazine and 3.0 Gm. hexamethonium chloride, her blood pressure quickly fell to an average of 140/90 mm. Hg. She was discharged from the hospital with this maximum dosage to be taken according to our usual regimen in which the amount of blocking agent is determined five times a day by reading the sphygmomanometer. Within a month the side effects of therapy had disappeared and she was leading a normal life. Gradually and automatically her hexamethonium intake decreased along with her blood pressure, and by September 1952, she only required 0.25 Gm. per day since her sitting systolic readings were almost invariably less than 130 mm. Hg and frequently below 120 mm. By this time we had reduced her daily dosage of hydralazine to .05 Gm. With cooler weather, however, her blood pressure rose to 150/100 mm. Hg, thus automatically increasing her mean hexamethonium requirement to more than 1 Gm. per day. By April of 1953, she needed no further hexamethonium ion. Shortly thereafter hydralazine was also discontinued. After an interval of three weeks her normal mean systolic pressure slowly rose to 155 mm. Hg, reaching 180 mm. on one occasion. Subsequently, small amounts of reserpine rapidly reduced her blood pressure to 125/75 mm. Hg. After discontinuation of this alkaloid, normotension persisted for two months without any antihypertensive agents. When it again increased a briefer course of reserpine was followed by a more extended period of strict normal blood pressure with no drug intake, which has continued seven months to date.

A PHYSICIAN: You mentioned some evidence that treatment of severe hypertension prolongs life and avoids disability. Would you elaborate?

DR. PERRY: The "malignant" stages of hypertension as previously defined are uncommon, but they serve to show the efficacy of therapy. Several series of patients with such an accelerated phase of the disease have been followed, indicating the dire prognosis without treatment. In the most recent compilation, Schottstaedt and Sokolow found that in the absence of therapy the average life expectancy was nine months, with almost half of the subjects succumbing in 90 days and only 15 per cent surviving for two years. Before effective drugs were available, Smithwick demonstrated a significant reduction in mortality among patients subjected to surgical sympathectomy as compared with a similar unoperated group. More recently, Smirk has shown a similar improved prognosis following treatment with autonomic blocking agents alone. Among 64 of our patients who were initially in the "malignant" stages of hypertension and who have regularly taken oral hydralazine and hexamethonium chloride over a two to four year period, 54 are alive and 51 are back at gainful occupations. It is difficult to see how such figures can be discounted or how a case history like the following can be ignored.

I. M., a Negro woman, was 47 years old when we first saw her in August, 1951. Two years previously she became totally incapacitated by intermittent but increasingly severe bouts of left ventricular insufficiency; and three years before that, she was denied life insurance because of albuminuria and hypertension. When she entered Barnes Hospital, she had long been unable to lie down, despite salt restriction and full digitalization. Fundoscopic examination revealed hemorrhages, exudates and papilledema. The other significant physical findings included bilateral pleural effusions, cardiomegaly, hepatomegaly and pedal edema. Her renal status was defined by 2 plus albuminuria, a normal blood nonprotein-nitrogen level, and 5 per cent excretion of intravenously injected phenol red in 15 minutes. Hydralazine and hexamethonium therapy according to the usual regimen dramatically lowered her mean blood pressure to less than 140/90 mm. Hg, where it remained for two years during which she regularly took her medication. During this interval, she was entirely free of symptoms including side effects of the drug and she daily worked 8 to 10 hours in a restaurant. Her ocular fundi became grade I (Keith-Wagener), her albuminuria disappeared and her cardiac size reverted to normal. Despite discontinuation of her digitalis and salt restriction, there was no recurrence of heart failure and she was accepted for insurance by the company which had rejected her seven years earlier. Unfortunately, she has since become careless in following her dosage schedule with several resultant bouts of hypertension which have been incompletely controlled by increased amounts of drugs.

A PHYSICIAN: How about cerebral vascular disease even when the blood pressure is adequately controlled?

DR. SCHROEDER: There is no tendency to cerebral hemorrhage when the blood pressure is well controlled. Cerebral thrombosis, on the other hand, can probably occur when normotension is induced too fast. When we began to use antihypertensive drugs, we saw three such episodes in patients whose blood pressures were

being rapidly brought down to low levels for the first time. We have not had another for several years. The statistics to date are inadequate to indicate whether or not cerebral thrombosis is prevented. In our series no thromboses have developed in patients who were well treated, even though such accidents may have occurred before treatment. When cerebral vascular disease is diffuse with mental deterioration, we have seen no improvement. The control of excessive vasospasm merely allows nature to take its course without the insult of hypertension.

A PHYSICIAN: What about the effect of treatment on the course of atherosclerosis?

DR. SCHROEDER: It is too early to tell. Blood cholesterol levels usually fall rapidly and remain lower for years in most patients taking hydralazine. What this means, we do not know. Angina pectoris usually gets better but occasionally becomes immediately worse, probably on a hemodynamic basis. When we can diagnose atherosclerosis for sure in its beginning, we may be able to judge the effects of treatment on this phase of the problem.

A PHYSICIAN: Heart failure is reported to account for over half of the deaths in patients with sustained hypertension. Is the treatment of hypertension of value in the presence of this complication?

DR. PERRY: Heart failure has almost disappeared as a cause of death in our series of patients. A failing left ventricle can be dramatically relieved by parenteral autonomic blocking agent, provided that elevated blood pressure contributes significantly to the cardiac load. This is true, regardless of the other contributing causes of the heart failure. Such relief is gratifyingly permanent in that only a handful of our previously digitalized patients treated with oral hydralazine and methonium compounds continue to need digitalis. Some of these points are illustrated in the fourth case history.

A PHYSICIAN: What limitations does azotemia or uremia place on drug therapy?

DR. PERRY: Slight azotemia is compatible with an excellent clinical result. On the other hand, lowering the blood pressure in the presence of unequivocal uremia only hastens the certain demise. We have found drug therapy useful, if the nonprotein-nitrogen level on admission to the hospital does not exceed 60 to 75 mg. per 100 ml. of blood. A nonprotein-nitrogen level much greater than 100 mg. per 100 ml. indicates so much renal damage that any diminution in glomerular filtration pressure often quickly proves fatal. The efficacy of treatment in the intermediate group depends upon many factors, including the intelligence and cooperation of the patient as well as the ability and perseverance of the physician. Although we have not produced nitrogen retention where it did not previously exist, it is usual for azotemia to be temporarily worsened as the blood pressure falls. With severe renal insufficiency, it is necessary to compromise and forego strict normotension. It must be remembered that methonium compounds are apparently not metabolized in the body; whatever is absorbed must be excreted by the kidney. Renal decompensation may convert one-half to one-eighth of the usual therapeutic intake into an effective dose. There is no known contraindication to using hydralazine in the presence of azotemia. The sole function of antihypertensive drugs is to lower blood pressure. They prevent further ravages of hypertension, but they do nothing to heal damage already produced. Nonetheless, after a period of months or years of lowered blood pressure, there is an unexplained and not inconsiderable improvement in renal function. The following case report shows how skill and infinite patience on the part of a house officer controlled the blood pressure of an azotemic patient in a range high enough to allow adequate glomerular filtration and low enough to control the heart failure from which he suffered.

H. M., a Negro man, was 50 years old when he was first admitted to Barnes Hospital in August, 1953. Although hypertension had been recognized three years previously, symptoms had begun six weeks before entry with the appearance of paroxysmal nocturnal dyspnea, ankle swelling, anorexia, nausea, vomiting and a weight loss of 15 pounds. Fundoscopic examination failed to reveal hemorrhages, exudates or papilledema. There were rales in the bases of both lungs, and clubbing of the fingers and toes was present without cyanosis. His blood pressure was 210/130 mm. Hg and his heart was enlarged with a diastolic apical murmur and a presystolic gallop. Hepatomegaly and pedal edema were noted. The abnormal laboratory data included 2 plus albuminuria and a nonprotein-

nitrogen level of 63 mg. per 100 ml. of blood. In view of his limited intelligence, the presence of azotemia, and the absence of the ocular stigmata of "malignant" hypertension, only digitalis, dietary salt restriction and reserpine were prescribed.

He was readmitted after seven weeks because of reappearance of both right and left ventricular failure. The changes in his physical examination were confined to the ocular fundi and included hemorrhages, exudates and papilledema. The only significantly altered laboratory finding was a nonprotein-nitrogen level of 109 mg. per 100 ml. of blood. Cautiously given hexamethonium chloride resulted in a fall in his blood pressure from its admission value of 240/140 to 190/115 mm. Hg. There was an immediate improvement in the signs and symptoms of cardiac decompensation and a concomitant rise in his nonprotein-nitrogen to 160 mg. per 100 ml. of blood. Maintenance of this blood pressure for a few days was accompanied by a fall in the azotemia to its admission level. Therefore the blood pressure was further slowly lowered to 170/100 mm. Hg and this was followed by a second increase in the nonprotein-nitrogen level to 125 mg. per 100 ml. which then gradually declined to less than 50 mg. where it remained. At the same time the last evidences of cardiac failure vanished. After almost two months of hospitalization, he was discharged with this minimal azotemia and compromise blood pressure. His medication was taken by mouth five times a day and consisted of a constant dose of 0.10 Gm. hydralazine and a simultaneous variable dose of hexamethonium chloride averaging 0.49 Gm. Unfortunately he discontinued his regimen because of absence of symptoms and a month later died of cardiac failure, a few hours after his final readmission to the hospital.

A PHYSICIAN: You said you had never seen a patient really resistant to these drugs. That may be so, but what is your actual experience, taking into account all of the factors involved, cooperation, side effects, late toxicity, etc.?

DR. PERRY: On the whole, it is good. About 80 per cent of our patients with severe hypertension control their systolic pressures at levels of 160 mm. Hg or below in four readings out of five. Few patients who need treatment cannot be encouraged by the physician to weather successfully the initially rigorous regimen and achieve lasting benefit. Private patients fare better than ward ones, and white patients better than Negroes. We do better than house officers, perhaps because we persist in treatment and handle side effects as they appear. We have an impression that the hardest therapeutic problems, barring azotemia, occur in men from 40 to 60 years old with "benign" hypertension and tortuous aortas. The next most difficult are the women with extreme emotional lability; partial autonomic blockade does not prevent spikes of blood pressure, induced by emotion and troughs, following relaxation; reserpine helps. A comparatively easy problem is the young "malignant" hypertensive without nitrogen retention.

A PHYSICIAN: Although there are some reports of very favorable results following these drugs, there are many who feel that drug therapy has little to offer hypertensive patients. Can you explain this discrepancy?

DR. PERRY: The conflicting reports regarding these drugs are disturbing. First, however, the areas of agreement should be emphasized. Although different investigators have used different drugs in different ways, those who have used them in adequate doses and according to logical schedules agree that the progress of severe hypertension has been halted or markedly retarded in many cases. As has been previously discussed, our definite claims of prolonging life have been confined to that small group of patients with "malignant" hypertension and a desperate immediate prognosis. I know of no contrary claims by an investigator using similar dosages for similar patients. Beyond the area of agreement, there are considerable areas of disagreement as to the efficacy of medical therapy. Several factors must be jointly responsible for the differences of opinion. The difficulty in evaluating the severity of human hypertension is not to be underestimated. Many physicians who do not believe in antihypertensive therapy insist that its good results are found only in those patients who are mistakenly classified as having bad hypertension. When a physician's skepticism as to the value of therapy is combined with an excessive fear as to its potential risk, he usually resorts to doses of insufficient size and frequency. This is unfortunate, since partial treatment often has no significant effect, and yet antihypertensive agents are commonly abandoned on the basis of such an inadequate trial. Unjustified expectations by the patient may be at fault. Many are not helped by drugs

because they expect too much and hence they are unwilling to tolerate temporary unpleasant side effects. Too many physicians are alarmed to see a sphygmomanometer in the hands of the public. Whatever the theoretic disadvantages of giving a blood pressure machine to a patient, the dangers of not doing so are very real. Ganglionic blocking agents are potent drugs. Sufficient must be given to achieve the desired antihypertensive effect, but hypotension-producing excesses should be avoided. The most satisfactory way to do this on a chronic basis involves giving the patient a sphygmomanometer and teaching him how to use it. We were fortunate in first giving the combination of hydralazine and hexamethonium chloride to four "malignant" hypertensive subjects, including the subject of the fourth case report, who were obviously rapidly deteriorating. To see three of these leave the hospital and return to gainful occupations was sufficient to counteract several succeeding failures.

A PHYSICIAN: Are patients not made neurotic when they are taught to determine and record their own blood pressures?

DR. PERRY: I have never seen a patient, who had achieved normotension, made nervous or neurotic by taking his own blood pressure, although I have seen a few who became tired of the routine and stopped it. The situation seems analogous to a diabetic testing his own urine. Elevated blood pressure is not alarming when it can be rapidly and safely lowered to any desired level. In fact, observing an elevated pressure fall following a pill instills a sense of security. It is true, of course, that they become as "blood-pressure conscious" as are diabetics "sugar conscious."

A PHYSICIAN: What type of patient would you not treat with these modern drugs?

DR. SCHROEDER: There are probably only three types of patients who do badly. The first is the uncooperative individual who refuses to take pills at stated intervals and who will not or cannot learn to take his own blood pressure. When the disease is serious or in "malignant" stages, giving potent drugs intermittently and ineffectually is tantamount to allowing rapid progression with eventual fatal outcome. In such cases, one has recourse only to surgical sympathectomy in an attempt to prolong life. The second kind of patient is the one with severe azotemia. We have 16 individuals with moderate nitrogen retention who are alive after three years; however, when frank uremia or marked azotemia is present, these drugs are almost valueless. Although they may relieve the workload of the heart and avoid pulmonary edema, the inexorable course of the disease is not halted. Whenever nitrogen retention is present, it is possible to lower the blood pressure beyond the point where adequate glomerular filtration through damaged kidneys can occur. In such situations, particularly after cardiac decompensation has occurred, it may be difficult to steer between the Scylla of heart failure and the Charybdis of renal failure, but by careful attention to detail it can be done. The third kind of case which should not be treated is the person with systolic hypertension on an atherosclerotic basis who has a normal diastolic pressure. These drugs act merely on excessive vasospasm. They do not act on hard pipes. Atherosclerotic individuals with a blood pressure of say 200/80 mm. Hg may achieve a blood pressure of 140/30 mm. Hg, but such a hemodynamic situation is hardly compatible with a good state of health. We are treating vasospasm and thereby affecting the general health of the patient. We are not treating a number.

A PHYSICIAN: What kind of patient is apt to respond to reduction of sodium in the diet?

DR. SCHROEDER: In our experience the best responses to sodium reduction are in women with central obesity, some disturbance of their generative organs, a history of a rapid gain in weight and low sodium or chloride concentration in sweat. So far nine of these women have come to autopsy or have been operated upon, and all but one have shown adrenal cortical adenomata; the other had pituitary basophilia. These patients apparently form excessive amounts of salt-retaining hormone and may represent a variation of primary aldosteronism. In general, we use hydralazine and methonium compounds since they do respond to these drugs, although some appear resistant at first. We, therefore, rarely need sodium restriction in them.

A PHYSICIAN: Why do you not use sodium restriction in all cases?

DR. SCHROEDER: Not only is it very inconvenient for the patient but there may also be an element of danger to it. When hydralazine is being given restriction of sodium in the diet may result in the "low-salt syndrome" or salt depletion in some patients. Apparently, hydralazine is a salt losing agent for kidneys that already show a tendency to lose salt, as hypertensive kidneys may. We have seen sodium depletion occur often enough to be thoroughly aware of its dangers when hydralazine is being employed.

A PHYSICIAN: What about the treatment of hypertension in pregnant women?

DR. SCHROEDER: I think that these cases must be divided into two types. First, in hypertensive women who become pregnant there is no contraindication to treatment. We have had very little experience with pregnancy in previously hypertensive women who were on these drugs, inasmuch as most of our patients are in the older age groups. For example, we have seen one patient who had two miscarriages in the past, who delivered a stillborn infant at six months, later delivered a premature but normally developed infant who lived for about 30 hours and is now pregnant again. So far no surviving babies have been born to pregnant women taking these drugs under our care. The second type of case is that in which toxemia of pregnancy appears. In such situations antihypertensive drugs may be lifesaving, lowering the blood pressure to reasonable or normal levels and allowing regression of the secondary effects of cardiovascular and renal strain. Patients can be carried in such situations until either delivery or operative intervention.

A PHYSICIAN: You mentioned delayed toxicity from some of these agents. Could you be more specific?

DR. PERRY: Two separate clinical entities have been reported, one resulting from hydralazine and one from hexamethonium chloride. The first occurs in about 10 per cent of patients who take 0.5 Gm. or more of hydralazine daily for at least six months. It is rare when smaller amounts are ingested. At its mildest, the syndrome consists of arthralgia and laboratory findings, usually associated with hepatic disease; in severer forms, it simulates acute rheumatoid arthritis; while the fully developed picture is indistinguishable from disseminated lupus erythematosus. Confirmation of the diagnosis is obtained from the elevated cephalin-cholesterol flocculation and thymol turbidity of the serum. Fortunately the process is reversed when the offending drug is stopped. No permanent sequelae have persisted and no fatalities, except those resulting from the recrudescent hypertension have been observed.

Hexamethonium toxicity is much less frequent and well defined. Pathologically it is characterized by a peculiar interstitial fibrosis of the lungs. We have only observed it in azotemic patients with the "malignant" stages of hypertension. It, too, apparently follows an extended and larger than average drug intake. It is recognized clinically by extreme tachypnea with surprisingly few concomitant pulmonary symptoms or signs. Breathing is characteristically improved, not worsened, by the supine position. Roentgenograms of the chest have been confusing and led to varied diagnoses. For the last 30 months we have not recognized this syndrome clinically, perhaps because of greater skill in using autonomic blocking agents.

A PHYSICIAN: Your remarks on toxicity disturb me. How can I avoid it in my patients? Do I have to watch them at very frequent intervals?

DR. SCHROEDER: It is relatively easy. If one examines patients at three-month intervals and advises them to watch for the warning signs of arthralgia, which usually bring a patient to a physician anyway, and then tests for the cephalin-cholesterol flocculation or the thymol turbidity of their blood, one can pick up "hydralazine disease" before it becomes advanced. Reducing the dose of hydralazine to small quantities or omitting it entirely will cause rapid reversal of symptoms. Our largest problem is in those patients who cannot take hydralazine and whose hypertension has recurred in spite of the use of large or even abnormal doses of ganglionic blocking agents and reserpine. One can avoid the toxic reactions of the ganglionic blocking agents, particularly the interstitial pneumonia, by treating the patient

adequately: in other words, by controlling the blood pressure well and not allowing wide swings to occur. A follow-up of the patient at three to six-month intervals is usually enough to avoid these uncomfortable and distressing reactions. However, in the treatment of hypertension, as in the treatment of diabetes, the patient must be educated both as to the actions of the drugs and to the disease itself in order that he may intelligently manipulate his therapy and achieve a return to a state of health desired by treatment of any chronic disease. It is our impression that physicians are either too fearful of these drugs or are not concerned enough with their primary actions and use them without respect for their potency. A happy medium between a knowledge of hypertension and knowledge of the drug is essential. I believe that any physician who can treat and control severe diabetes can treat and control hypertension with modern agents.

A PHYSICIAN: Why don't we use the mildest acting and safest drugs in all cases and avoid risk?

DR. PERRY: Because the aim of treatment is to achieve normalcy. To give reserpine alone or a low salt diet to a patient rapidly advancing into uremia is similar to treating diabetic coma with diet or pneumonia with cupping. Mild cases need only mild drugs; severe cases require the most potent ones in doses large enough to produce the effect desired. We must use everything we have to stop the process, and use our heads when we do it.

A PHYSICIAN: What is the rationale for combining ganglionic blocking agents and hydralazine? It seems to me that some reports on the use of hydralazine alone were disappointing, while some people were optimistic about ganglionic blocking agents used alone.

DR. PERRY: We use both because in our hands the combination has proved the most effective therapy available. It is true that hydralazine alone frequently does not lower blood pressure significantly and only rarely produces normotension. On the other hand, although ganglionic blocking agents by themselves almost always lower blood pressure initially, control is usually very irregular and tolerance seldom fails to develop quickly. Having frequently observed the initially successful therapy become increasingly less valuable, we searched for a possible explanation. The most reasonable suggests that after human hypertension has exceeded a certain degree of severity, it is rarely of purely neurogenic origin. Ordinarily, there is a renal component as well. Our present concept is that hydralazine counteracts the renal factor, whatever it may be; whereas ganglionic blocking agents affect the autonomic nervous system, or neurogenic factor.

DR. SCHROEDER: Hydralazine is a unique drug with several fundamental actions about which we know very little. Dr. Perry has discovered that some of the antihypertensive agents not acting on nerves inhibit dihydroxyphenylalanine decarboxylase, an enzyme which contains pyridoxal phosphate and presumably a trace metal. Furthermore, hydralazine enhances the action of monamine oxidase, a property shared by some other chelating agents. It is possible that the drug may affect certain enzyme systems concerned in the relief or prevention of excessive vasospasm. Further to stimulate our imagination, there is a substance, described some 15 years ago, which we named pherentasin. It is a long-acting vasoconstrictor substance procured from human hypertensive arterial blood. To date it would appear to be a primary amine, possibly a polypeptide. We have recently been able to detect its presence in small amounts of venous blood by using a spirally cut rabbit's aortic strip suspended in oxygenated Krebs-Ringer solution. A sustained constriction occurs when pherentasin is added to the water bath. This substance has certain peculiarities in regard to trace metals and metal binding agents. In the first place, its activity is completely destroyed by such compounds as hydralazine, thiocyanate, ethylenediamine tetra-acetate, 8-hydroxyquinoline, nitroprusside and sodium azide, all of which show some antihypertensive properties in man or in animals. Furthermore, manganous ion is the only metal tested that destroys pherentasin in vitro. When this substance is demonstrated in the blood of hypertensive patients and their blood pressures are then controlled with hydralazine, the substance can no longer be found. Because extraneous metals have been found in

human kidneys and urine, we speculate that some nonessential metal is inhibiting a metalloenzyme in the kidney, the nature of which is unknown but which is concerned in the alteration of intermittent vasospasm into permanent vasospasm and eventually produces organic changes in the kidney which maintains the blood pressure high. Hydralazine attacks that mechanism. These are our ideas to date and the use of two differently acting drugs appears logical in their light.

A PHYSICIAN: You mentioned previously that after a long period of therapy some of these patients can take considerably less drug than at first. Dr. Wilkins, in his recent article in the Journal of Chronic Diseases, implies the same. Do you actually believe that the basic process of hypertension is being reversed?

DR. SCHROEDER: We do. The evidence is not yet conclusive but it appears from the clinical measurements that one can make that the underlying process is reversing itself very slowly in well treated patients. It also appears that the underlying process is not reversing itself in partly treated patients. Those whose blood pressures are well controlled eventually need only a fraction of their original dose of drug or perhaps need only a small amount of reserpine whereas two to three years previously they had required large doses of ganglionic blocking agents, reserpine and hydralazine, to achieve control. Those individuals have shown an improvement in the electrocardiogram often to normal, a diminution in the size of the heart, which comes very slowly after two years or more, and, what has been more striking, an improvement in renal function toward or to normal, a totally unexpected finding. The evidence is accumulating that the secondary effects of hypertension are changing in the direction of normal and, possibly, that the underlying disease process itself is slowly reverting to a normal state in that less and less of the drug is being required.

A PHYSICIAN: Would you elaborate on your ideas regarding the etiology and pathogenesis of hypertension in the light of the primary actions of these drugs?

DR. SCHROEDER: While it has not yet been adequately proven that the sympathetic nervous system is overactive in arterial hypertension, three of the four types of drugs which have been mentioned act upon the autonomic nervous system. While it is possible that a normal tonus of the sympathetic nervous system is present in hypertension, the evidence is to the contrary. We have not time to list the evidence which, although indirect, points to overactivity. Let us say, then, that certain persons in the population have the ability to react to stress by vasospasm, either because of inherited or developmental traits. These persons may show a positive cold pressor test even though they are normotensive. As has been well worked out by Hines, many of them develop hypertension 10 or 20 years later. If this is so, a certain proportion of the population is predisposed to hypertension. It is only through nervous mechanisms that these reversible reactions can take place and one must assume that the sympathetic system plays the major role. Now the crux of the whole matter of pathogenesis, the "64 dollar question," seems to be: What factor or factors convert temporary intermittent vasospasm into permanent vasospasm? From epidemiologic studies, it would appear that there may be something in our civilization which tends eventually to convert reversible neurogenic vasospasm into irreversible or permanent vasospasm. In view of the tremendous amount of work on the kidney and its relation to sustained hypertension in animals and man, our suspicions are naturally directed to that organ. However, it has been shown conclusively, both experimentally and clinically, that organic renal arteriolar disease follows and does not precede the development of chronic hypertension. In dogs, the lesions may not appear until the fourth or fifth year of sustained hypertension. Therefore, we cannot implicate an organic renal basis. What other basis is there? We may look upon certain renal enzymatic mechanisms as being possibly affected by some exogenous material in civilized areas. Our suspicions became naturally aroused when it dawned upon us several years ago that all of the agents used to treat hypertension had in common only the ability to bind trace metals. Hydralazine was found by Dr. Perry to do this; thiocyanate is a commercially useful material for purification of

ores; nitroprusside, 2,3-dimercaptopropanol (BAL), and certain other mercaptans are specifically depressor in animals; sodium azide has a similar rather transient effect; 8-hydroxyquinoline and ethylenediamine tetra-acetate are antihypertensive in rats; and certain thiopseudoureas and thiosemicarbazide have this common property. All appear to act specifically upon hypertension, either experimental, clinical, or both. The discovery by Tipton and her associates of large amounts of presumably abnormal trace metals in American human tissues has led to considerable speculation and to some experimental work. The startling finding of Tipton and her co-workers was the presence of an enormous amount of cadmium in the human kidney, up to 33 mg. per kilogram. Cadmium did not appear in several infants, was there in smaller quantities in an older child, but was present in all adults studied. We do not know how it got there, but its concentration was half that of essential zinc. Truly it appears that trace metals may be involved in hypertension and the best lead we know of lies in their removal from the body by better chelating or binding agents.

A PHYSICIAN: You have implied that hypertension is no longer a problem in your patients. Is that so?

DR. SCHROEDER: Within the limits we have stated, that is true. Our cooperative patients are no longer dying of its secondary effects, congestive heart failure and uremia. What deaths we have are usually the results of atherosclerotic thromboses of coronary or cerebral vessels. Atherosclerosis is now clearly the culprit.

A PHYSICIAN: What about the newer drugs? We are now and probably shall be in the future invited by advertising claims, both direct and indirect, to believe that this or that agent or combination is the answer to our problem. Would you care to draw any general conclusions as to the general efficacy of drug therapy for hypertension in the future?

DR. SCHROEDER: It is proper to do a little theorizing and predicting. Bearing in mind the dual or triple pathogenetic mechanisms operative in severe hypertension, one can safely say that no agent acting solely upon autonomic nerves can ever be more effective than *total* sympathectomy. Therefore, newer ganglionic blocking agents may be more readily absorbed, act more on sympathetic than on parasympathetic functions, act for longer intervals and more evenly, produce fewer side effects, be more potent on a weight for weight basis and be preferred to the older, time tested drugs. While the effects of their use in milder stages of the disease may be excellent, it is unlikely that they can do better than permanent surgical removal of nerves. Very long acting sympatholytic agents may be developed which will be free of serious side effects, but the same statement holds true. For those acting on the mid-brain, of which many will be discovered, now that the door of specific action has been opened by reserpine and chlorpromazine, no agent can be more effective than the relative influence which the mid-brain bears to the total picture.

It is our belief that reversal and, perhaps, eventual cure can be only accomplished by drugs which will do what hydralazine does basically. Therefore, much time and effort must be spent to understand its fundamental actions. Sympathetic nerve blockade alone will be limited to mild stages, but severe cases need a double-barreled approach. The day when one specific drug will control all cases without careful supervision is far distant.

CONCLUDING REMARKS: Modern antihypertensive drugs require intelligent handling by both physician and patient. When so employed, the results are usually gratifying to the patient. As a first approximation of specific treatment, they are the best we have. In spite of our overstressing their toxicities, actually they are much less hazardous than some popular drugs and their use is well-justified by the seriousness of the disease which they can control. Fatalities due to the drugs themselves are rare. Their side effects which vary with their potencies are sometimes distressing but seldom require discontinuation. There are enough drugs now available to control the hypertension and promote longevity of almost any patient who wants to be treated and will submit to therapeutic inconveniences.

CLINICAL PROGRESS

Acute Pulmonary Edema

Pathology, Physiology and Clinical Management

By A. A. LUISADA, M.D. AND L. CARDI, M.D.

Acute pulmonary edema may be associated with the most varied clinical conditions including cardiovascular, renal, cerebral, and pulmonary diseases, trauma to the skull or chest, infections, and shock. Many drugs and physical means have been employed in the treatment of this syndrome. Two main clinical types of pulmonary edema may be differentiated because of the different effect of therapy in each of them. Antifoaming therapy, a purely symptomatic method of treatment, tends to break a vicious circle and may be lifesaving. It should be employed initially while the patient is being examined and drugs or other remedies are being selected for possible additional treatment.

NO BETTER definition of edema of the lungs can be given than that of Laennec[1] (1834): "Edema of the lung is the infiltration of serum into the substance of this organ, in such degree as evidently to diminish its permeability to the air, in respiration." While edema of the lungs is initially similar to edema of other organs, the structures surrounding the capillaries are so thin that an immediate outpouring of fluid into the alveolar cavities* occurs. In this respect, pulmonary "edema" is followed by pulmonary "exudation."

The term "pulmonary edema" carries with it different associations to different specialists: to the pediatrician, acute glomerulonephritis or rheumatic carditis; to the surgeon, thoracic or abdominal intervention; to the neurologist, cerebrovascular accident or trauma to the skull; to the cardiologist, hypertension, coronary occlusion or mitral stenosis.

ETIOLOGY

Contrary to a widely accepted view, acute pulmonary edema can be encountered in a great variety of conditions, as shown by necropsy findings (table 1). The frequency of pulmonary edema in the various diseases is indicated in table 2. A more detailed study of the various conditions which may be associated with acute pulmonary edema is presented in table 3.

A large number of clinical cases succumb without pulmonary edema; this disorder, therefore, is not a "terminal" or "agonal" phenomenon to be considered as the necessary precursor of death.

A brief review of the most common causes of pulmonary edema in clinical cases follows.

(1) *Pulmonary Edema and Arterial Hypertension.* This type of pulmonary edema was in the past most common[3] but is now seen less frequently, partly on account of more effective treatment of various clinical conditions, and partly because other types tend to predominate. Chronic nephritis with *uremia* is frequently accompanied by episodes of edema of the lungs. In certain cases, moderate nitrogen retention may be the only evidence of renal insufficiency and there may be little or no acidosis. All other forms of hypertension, including essential hypertension and that of coarctation of the aorta, may present pulmonary edema. Cases with malignant hypertension have these paroxysmal attacks more commonly than others.

(2) *Pulmonary Edema and Coronary Heart Disease.* The observation that severe coronary occlusion is frequently accompanied by pulmonary edema has led to the belief that minor coronary episodes may also contribute to these

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* To a more limited extent, fluid also appears in the pleural cavities.[5]

TABLE 1.—*Main Necropsy Findings in 100 Unselected Cases of Pulmonary Edema (from Cameron[2])*

Pathology	No. of Cases
Severe coronary disease	34
Congestive failure	32
Carcinoma of various organs (carcinoma of lungs = 15 cases; obstruction of pulmonic veins = 11 cases)	27
Bronchopneumonia	23
Hypertensive heart disease	18
Massive pulmonary embolism	10
Cerebral hemorrhage	9
Cerebral tumor	7
Tuberculosis	6
Liver cirrhosis	6
Fractured skull	3
Multiple fractures (excluding skull)	2

attacks. However, no certain proof has been presented, and the mechanism of production of the edema might be somewhat different from that in hypertensive patients. Cardiogenic shock is more frequently associated with pulmonary edema than other types of shock. Protracted forms are common in coronary heart patients.

(3) *Pulmonary Edema and Cerebral Diseases.* The occurrence of pulmonary edema in cases of meningitis, encephalitis, or brain tumor is relatively common, in children as well as adults. Cerebrovascular attacks, including hemorrhage, embolism, or thrombosis, and subarachnoid hemorrhage, as well as trauma to the skull, are frequently followed by pulmonary edema. Undoubtedly, coronary lesions and preexisting hypertension may be contributing factors in certain cases. However, in others, no evidence of such lesion or disorder can be demonstrated clinically following recovery, or at autopsy.

(4) *Pulmonary Edema and Pulmonary Heart Disease.* Contrary to current opinion, this association is far from rare. Pulmonary edema may follow *pulmonary embolism.* Occlusion of a stem of the pulmonary artery causes increased flow in the other, and this may favor high capillary pressure in one lung. Even occlusion of smaller branches may cause diffuse, bilateral edema, a fact which has led to numerous speculations. In *chronic cor pulmonale* with right ventricular hypertrophy and pulmonary hypertension, acute pulmonary edema may develop. This is particularly true in the forms causing no destruction of capillaries and no pulmonary ischemia.

It is likely that vascular obstruction or destruction of a number of vascular districts (fibrosis, emphysema) favors pulmonary edema of other areas and districts. It is known that one-half of the pulmonary vessels can carry the entire flow of the lesser circulation without any increase in pressure. However, this is obtained through distention of the normal vessels which, in itself, predisposes to edema. Whenever an increase of venous return takes place in such patients, the already distended (normal) vascular districts are taxed beyond physiologic limits and transudation is likely to occur. In addition, sudden pulmonary edema was observed in cases with deformity of the chest (pulmonocardiac failure of Chapman, Dill and Graybiel[23]). It is self-understood that, whenever other causes of pulmonary edema are present, this condition may develop in cases of chronic cor pulmonale like in others. This particularly applies to systemic hypertension and coronary heart disease. Anoxia would favor the edema; narrowing of arterioles would decrease its severity, at least in the involved districts.

(5) *Pulmonary Edema in Trauma to the Chest.* This syndrome, called by surgeons "traumatic wet lung," has been the object of considerable speculation and is of particular interest because of its spreading from the damaged to the intact areas of the lungs.

TABLE 2.—*Frequency of Pulmonary Edema in 500 Autopsies of Special Conditions (from Cameron[2])*

Pathology	Total No. of Cases	No. Showing Pulmonary Edema
Hypertensive heart disease (excluding chronic nephritis)	94	81 (86%)
Chronic nephritis	50	37 (74%)
Coronary occlusion	66	45 (68%)
Cerebral hemorrhage	66	44 (67%)
Mitral stenosis	84	55 (65%)
Fractured skull	38	24 (63%)
Multiple fractures (excluding skull)	28	17 (61%)
Pulmonary embolism	74	23 (31%)

TABLE 3.—*Clinical Conditions Associated with Acute Pulmonary Edema*

(A) Cardiovascular disease	1—Syphilitic heart disease (aortic insufficiency; aortitis; aortic aneurysm)
	2—Rheumatic heart disease (acute rheumatic carditis; mitral insufficiency; mitral stenosis; aortic insufficiency; aortic stenosis)
	3—Coronary heart disease (severe, acute coronary occlusion; minor occlusion plus extensive ischemia or fibrosis of the myocardium)
	4—Hypertensive heart disease (pheochromocytoma, essential hypertension; acute glomerulonephritis; hypertensive nephropathies, especially if there is uremia; toxemia of pregnancy)
	5—Congenital heart disease (coarctation of the aorta; atrial or ventricular septal defect, patent ductus; Eisenmenger complex; Lutembacher syndrome)
	6—Acute or chronic pulmonary heart disease (pulmonary embolism; chronic cor pulmonale)
	7—Shock (including that caused by exposure to x-ray radiation)
	8—Congestive failure
(B) Diseases or lesions of the central nervous system	1—Trauma to the skull
	2—Subarachnoid hemorrhage
	3—Cerebrovascular attack (hemorrhage, thrombosis, embolism, abscess or tumor)
	4—Encephalitis, meningitis, poliomyelitis, tetanus
(C) Diseases or lesions of respiratory system	1—Pneumonia, bronchopneumonia (especially influenzal)
	2—Drowning, strangulation, asphyxia, respiratory obstruction (edema of the glottis, bronchial asthma, foreign bodies)
	3—Inhalation of irritant or toxic gases (including those used in warfare); respiratory burns
	4—Following rapid thoracentesis
	5—Following trauma to the chest
	6—Following lobectomy
(D) Allergy	Angioneurotic edema; serum sickness; following injection of gold preparations; following inhalation of penicillin aerosol.
(E) Following stimulation of hollow viscera	1—Distention of esophagus, stomach, or gall bladder.
	2—Following too rapid emptying of distended bladder or ascites.
(F) Surgical and obstetrical cases	1—During pregnancy or after labor (especially, but not only, in cases with rheumatic heart disease, eclampsia, or toxemia)
	2—Following transfusions or infusions (especially, but not only, in cardiac or anemic patients)
	3—Following surgical manipulation of stellate ganglia
(G) Toxic	Following use or overdose of thiourea derivatives, iodides, muscarine, eserine, prostigmine, opium, methyl salicylate, acetic and butyric ether, phenylcarbamide.
(H) Miscellaneous	Thyroid crises. Beriberi. Insulin shock. Burns.

(6) *Pulmonary Edema in Mitral Stenosis.* The occurrence of pulmonary edema in cases with a persistent block proximal to the left ventricle contradicted the established theory which attributed these episodes to acute left ventricular failure. It is only in recent years that an adequate dynamic explanation has been found. Patients with mitral stenosis occasionally cough up large amounts of pure blood. This syndrome, called "pulmonary apoplexy," is closely related to pulmonary edema and has a similar, though not identical, mechanism.

(7) *Pulmonary Edema and Infections.* It has been clearly established that pulmonary edema and pneumonia may be closely interrelated. Pneumonia may predispose to pulmonary edema and vice versa; furthermore, they may simulate each other. Many other febrile diseases may be complicated by pulmonary edema, partly through inflammatory lesion of the heart, lungs, or brain, and partly through overload of the circulation caused by therapeutic intravenous infusions. Unexplained edema of the lungs may also develop during the chill phase of a febrile reaction.[110]

(8) *Pulmonary Edema and Shock.* Shock is frequently associated with pulmonary edema. It is not known whether shock itself causes pulmonary edema or whether both shock and pulmonary edema result from a common cause.

Since cardiogenic shock is frequently associated with pulmonary edema and the latter disappears when shock is alleviated, the vascular mechanism of shock is probably of fundamental importance.

The Clinical Episode

An attack of pulmonary edema may occur at any time of day or night. Precordial oppression or pain, restlessness, weakness, and dry, non-productive cough may precede the attack. If this occurs at night, a nightmare frequently precedes the paroxysm. *Respiration* becomes difficult and labored and is usually accelerated. The patient sits up in bed and may lean forward. Within a few minutes, gurgling sounds can be heard, and the patient repeatedly emits a white, yellowish or pink *frothy sputum*. This may vary from a few bubbles to enormous amounts (as much as 2000 to 3000 cc. of foam within one to two hours). Cold, clammy extremities, paroxysms of suffocation and vomiting may occur. The *pulse* and *blood pressure* differ in the two main types of attacks as follows:

(1) In most cases connected with coronary occlusion, pulmonary embolism or allergic shock, the pulse is rapid and small (and may be irregular), and the blood pressure drops gradually, sometimes reaching shock level. Some cases of rheumatic mitral lesion also exhibit a drop in blood pressure.

(2) Other cases, particularly those with hypertensive or syphilitic heart disease or those with a cardiovascular accident, present a full pulse and a blood pressure either equal to or higher than the previous level.

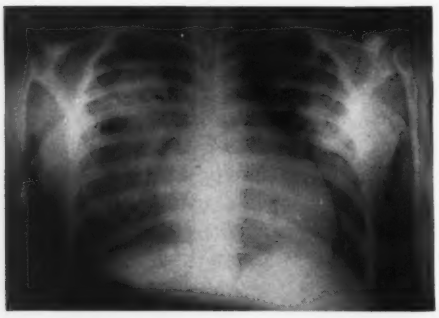

Fig. 1. X-ray film of the chest during pulmonary edema.

Physical examination reveals a high, tympanic percussion note over the lung fields and innumerable moist rales over the entire chest, which arise in the small bronchi, and gurgling sounds created by the foam in the trachea.

X-ray of the chest reveals extensive shadows in both lung fields (fig. 1).

The *temperature* is usually normal during the attack except with inflammatory edema, but may rise soon afterwards because of reabsorption of altered proteins from the lungs.

The *sputum* has a chemical composition similar to the fluid of angioneurotic edema or allergic coryza, and to the inflammatory effusions of large serosal cavities. This is true, not only of clinical episodes,[4] but also of experimentally induced attacks.[4, 5]

Catheterization of the right heart has revealed that pulmonary arterial pressure is severely increased and that pulmonary "capillary" pressure rises to 32 to 54 mm. Hg during the attack.[57, 47]

Experimental Pulmonary Edema

Experimental pulmonary edema has been obtained by using a great variety of methods.

(1) *Acute left ventricular strain* has been obtained by ligation of the aortic arch in the rabbit,[7] but this procedure is far from being constantly successful, especially if the chest is open,[8, 9] and cannot be duplicated in the dog.[21] *Acute right ventricular strain* has been provoked by inducing pulmonary embolism.[13, 72]

(2) *Acute ventricular damage* was obtained by reducing the left ventricular chamber[7, 10] and by necrosis of either the left[11, 12] or the right[12] ventricular walls.

(3) *Acute obstruction of the pulmonary veins* was tried in animals,[6, 9] but was not particularly successful.

(4) *A complex mechanism involving the cardiovascular and nervous systems* leads to pulmonary edema following the *intravenous injection of epinephrine*[14-16] or *l-norepinephrine*.[17] This procedure is consistently successful

in the rabbit, guinea pig and rat, but not in the dog or cat. A similar mechanism seems to occur in hypoglycemia.[73]

(5) *Trauma to the chest*[18] and *limited pulmonary embolism*[72] are of particular interest because they cause bilateral pulmonary edema in the dog.

(6) *Enormous doses of intravenous infusions*[19-22] or *rapid intracarotid infusion of somewhat smaller doses of saline or plasma* are successful in producing pulmonary edema in the rabbit,[23] cat[3] or dog.[3, 22]

(7) *Direct irritation of the bronchial tree* is obtained by inhalation of toxic gases,[26-24] or intrabronchial injection of hypertonic solutions.[3]

(8) *Toxic pulmonary edema* follows the injection of methyl salicylate,[27] muscarine[28, 29] or alloxan,[56] or the ingestion of thiourea derivatives[30, 31] or ammonium chloride.[32-34]

(9) *Cerebral damage or dysfunction* has been obtained through occlusion of the carotid arteries in the rabbit,[35, 36] trauma to the brain in the dog,[37, 38, 39] destruction of the hypothalamus in the rat[40, 41] or the intracisternal injection of veratrin[42] or fibrinogen plus thrombin[43, 44] in the rat, rabbit or dog.

(10) A combination of *stress applied to the left ventricle* (aortic insufficiency) *plus intravenous epinephrine or central nervous system stimulation* was successfully employed in the dog.[45] A similar result was obtained by *aortic insufficiency* plus *unilateral nephrectomy* and *contralateral narrowing of the renal artery*.[71]

Pathogenesis

The mechanism of production of pulmonary edema has been explained in different ways. Most writers have attempted to evolve one theory which might apply to *all* causes of pulmonary edema. It is the feeling of the authors that this is not feasible and that different mechanisms should be advocated.

The oldest theory, advanced by Cohnheim[19] and Welch[7] in 1878, postulates *acute left ventricular failure* causing a rise of pulmonary venous pressure and then pulmonary edema (fig. 2*A*). This theory met with wide acceptance and is even now currently invoked. Several objections can be raised:

(1) Many clinical cases of pulmonary edema have a normal left ventricle and the initial sequence of events involves either the central nervous system or the lungs. Some cases have severe mitral stenosis or cor pulmonale and the right ventricle is the cardiac chamber under strain.

(2) Many clinical cases with acute left ventricular failure die in shock (cardiogenic shock) without pulmonary edema. This is probably due to the fact that pulmonary capillary pressure rises only if there is good venous

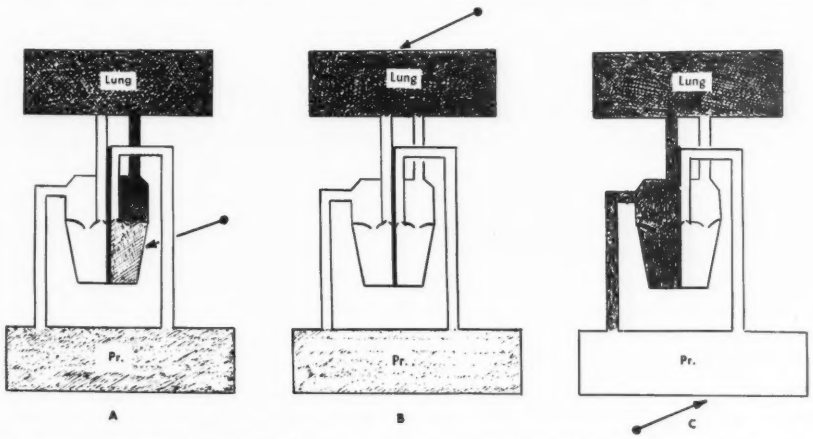

Fig. 2. Scheme of mechanism of pulmonary edema according to three theories. (*A*) Left ventricular failure (passive congestion). (*B*) Pulmonary vasodilatation (active congestion). (*C*) Peripheral constriction with pulmonary congestion.
[Pr. = periphery.

return to the right heart with a strongly active right ventricle.

A second theory was advocated by Teissier[46] in 1900. Disregarding cardiac elements, he considered pulmonary edema as due to *an active, sudden dilatation of the pulmonary vessels* (fig. 2*B*). Even though this theory could not be accepted, the importance of reflex changes of the pulmonary vessels has been emphasized by one of the authors (A.A.L.) and his co-workers,[3, 48, 49] as well as by Cameron and Kuo.[43] The following experimental data seem to confirm the importance of these reflexes in the production of pulmonary edema, even though they may also be interpreted according to other theories.

(1) Bilateral stellectomy is effective in preventing pulmonary edema caused by intravenous epinephrine in the rabbit.[48]

(2) Rapid infusions produce different results depending upon whether they are given intravenously or injected into the carotid arteries. Denervation of the carotid sinus area prevents this type of pulmonary edema.[49, 50]

(3) Anesthetics, sedatives and sympatholytic agents are more effective in preventing most types of pulmonary edema than vasodilators.[63]

Another theory was advocated by Peserico[3] in 1930 and revived by Sarnoff[44] in 1952. This "neurohemodynamic pulmonary edema" emphasizes the *massive displacement of blood from the greater to the lesser circulation* caused by strong sympathetic stimulation (fig. 2*C*).

Three elements should be considered of importance in the production of pulmonary edema.

(1) *High Pressure in the Pulmonary Capillaries.* This is usually the result of forceful cardiac dynamics. A sudden displacement of blood from the greater to the lesser circulation may favor the edema, especially in the presence of decreased reserve of the left ventricle or mitral block. Severe peripheral vasoconstriction may be caused by epinephrine (anger, fright, exposure to cold), angiotonin (renal ischemia), or vasomotor stimulation (central lesions, reflex stimulation). This vasoconstriction causes increased arterial resistance resulting in left ventricular strain on the one hand, and increase of venous return to the right heart on the other. This tends, therefore, to produce a high pulmonary capillary pressure through a dual mechanism.

High pulmonary arterial pressures are usually found in experimental pulmonary edema and were also observed in clinical cases through catheterization.[57] However, only a few such cases have been studied so far. Pulmonary edema, induced by inhalation of phosgene, fails to show pulmonary hypertension[51] and seems to have a different mechanism. It is theoretically sound to assume that pulmonary capillary pressures above 25 mm. Hg would lead to a transudation of plasma. However, much higher capillary pressures are required for causing pulmonary edema in animals, whereas pressures of 30 to 40 mm. Hg are not unusual in mitral patients without evidence of edema. Mitral patients experience a rise of pulmonary "capillary" pressure from 25 to 30 mm. Hg to 32 to 54 mm. Hg during an attack of edema. It is interesting to note that similar pressure increases are observed in either mitral patients or hypertensive patients in failure, during exercise tests without the appearance of edema.[47] Even though it is possible that minimal edema is quickly drained via the lymphatic vessels, it seems likely that other protective elements are also involved.

A close relationship exists between humoral and mechanical elements. This is well illustrated by the observation that *histamine* exerts a more powerful constrictive effect on the venules than on the arterioles of the lungs.[62] Thus histamine, by causing a marked increase of pulmonary capillary pressure, may be one of the contributing elements of pulmonary edema.

(2) *Increased Permeability of the Pulmonary Capillaries.* This is favored by increased pulmonary flow (leading to dilatation of the capillaries), allergy, poisons, anoxia, dyspnea (suction effect), chronic heart failure, inhalation of toxic gases. Speculations on whether capillary permeability may be altered by nerve impulses without concomitant changes of capillary pressure have not, as yet, been supported by conclusive evidence. There are,

owever, suggestive experiments, including ıe production of pulmonary edema without ulmonary hypertension through faradic stimuıtion of the stellate ganglion.[54]

The part played by specific substances in ıcreasing permeability has been the object f several investigations. The *histamine* content f certain organs, especially of the lungs,[58] is ıcreased after an injection of epinephrine.[58, 59] Large amounts of this substance are liberated during experimental pulmonary edema.[58, 60] *Corticotropin* (ACTH) decreases the mortality of animals from experimental pulmonary edema,[52, 80] and this has led to speculation that adrenal cortical hormones also play some role in the mechanism of the attack.[53, 80] This effect of corticotropin explains why different "*stress reactions*" inhibit pulmonary edema in animals.[52, 53, 80] The unexplained effect of *splenic substances* in favoring pulmonary edema of the rabbit[80, 105-107] might be interpreted as being due to increased permeability of the pulmonary capillaries caused by substances which are either formed by or are stored in the spleen.

(3) *Decreased Osmotic Pressure of the Blood.* This occurs after prolonged saline infusions, in lipoid nephrosis, starvation or liver diseases. The effect of this factor is widespread. Therefore, either pulmonary edema is part of a diffuse anasarca or is favored by other edematogenic factors.

A comprehensive work on pulmonary edema of 25 years ago[3] divided the factors of pulmonary edema into mechanical, neurogenic, and humoral. It is now possible to modify this view by recognizing that most elements are interrelated: chemical and endocrine products may cause vasoconstriction and changes of permeability; blood pressure changes may cause reflex release of hormones or chemicals; and neurogenic elements may act either through the vasomotor system or through hormones. Moreover, the part played by the various factors is different according to the various causes and associated elements of pulmonary edema.

Among the conclusions reached by experimental workers, the following have a special importance:

Extreme stimulation of the brain or the carotid body leads to *direct* or *reflex stimulation of the sympathetic system*, followed by severe vasoconstriction. This leads to increased peripheral resistance with increased loading of the left ventricle; displacement of a large mass of blood from the arterioles, capillaries, and blood reservoirs towards the veins; increased venous return; and, finally, filling of the blood vessels of the lungs with a large quantity of blood. In other words, this stimulation causes an increased output of the right ventricle, and, at the same time, increased difficulty in the emptying of the left ventricle. This mechanism assumes great importance if there is *left ventricular strain*, and even more so if there is *left ventricular failure*. Whether or not it is sufficient to cause pulmonary edema with an intact heart is still open to question.

The possible role of *vascular phenomena of the lesser circulation* in favoring pulmonary edema is still speculative. It is known that arteriolar constriction in the lungs is present in many clinical conditions associated with high pulmonary arterial pressure and prevents an excessive increase in pulmonary capillary pressure. *Any relaxation of these arteries would favor flooding of the capillary bed and edema.* Some of the possible causes of loss of arteriolar tonus, such as reflex vasodilation, direct effect of hormones, and direct effect of anoxia, still require investigation.

Anoxia causes a direct dilatation of the pulmonary vessels and a reflex (carotid body) increase of cardiac output.[55] *The combination of these two elements strongly favors pulmonary edema.*

The following considerations attempt to explain the various clinical forms of pulmonary edema.

(1) *Pulmonary Edema Following Massive Myocardial Infarction.* When the power of the left ventricle is suddenly decreased, there occurs a marked increase of left atrial and pulmonary capillary pressures. However, the latter persists only if adequate venous return is maintained. Therefore, a severe (but not too severe) lesion of the ventricle is the most effective. A peripheral mechanism initiated by cerebral ischemia, carotid-sinus hypotension or carotid-body

hypoxia, may contribute to the disturbance by causing peripheral vasoconstriction. The accumulation of blood in the lungs is, therefore, very probably due to both a cardiac and a vascular mechanism. The peripheral effects of *serotonin*, liberated in the area of infarct, are still speculative.

(2) *Pulmonary Edema of Patients with Hypertension, Aortic Insufficiency or Aortic Stenosis; of Cases with Minor Coronary Attacks; and Following Transfusion in Surgical, Obstetrical, Anemic or Cardiac Cases.* Left ventricular strain is followed by increase of left atrial and pulmonary venous pressures. Excitement, exposure to cold, fear of death or exertion, cause sympathetic stimulation and redistribution of the blood with its accumulation in the lungs, favoring thereby acute pulmonary edema. The increased peripheral resistance may transform ventricular strain into ventricular failure. Or else, transfusions or infusions, by directly increasing the volume of blood in the lungs and lowering osmotic pressure, further favor the edema.

(3) *Pulmonary Edema of Nephritic Patients, Especially if Uremic.* A mechanism similar to that of (2) can be postulated. Retention of metabolites increasing capillary permeability (nephritis) or decreased osmotic pressure of the blood (nephrosis) may be among the favoring causes.

(4) *Pulmonary Edema Following Trauma to the Skull or Lesion of the Central Nervous System.* In this type, there is severe central sympathetic stimulation. This causes vasoconstriction and increased resistance placing a severe load on the left ventricle; it also leads to redistribution of the blood and its accumulation in the lungs. While these elements favor pulmonary edema, other factors should also be taken into consideration such as dilatation of pulmonary vessels and liberation of substances increasing capillary permeability (histamine, hyaluronidase, etc.).

(5) *Mitral Stenosis.* The outflow of blood from the lungs is impeded by the mitral block, even during rest. Sympathetic stimulation caused by excitement, exertion, exposure to cold, anger or fright leads to: (a) *tachycardia*, with shorter diastole and impaired emptying of the left atrium; and (b) *vasoconstriction*, with redistribution of the blood and its accumulation in the lungs. The effect of the mitral block is proportionally increased by greater venous return to the heart.

(6) *Exposure to Toxic Gases.* Here the most important effect seems to be damage to the capillary endothelium followed by liberation of substances increasing capillary permeability. The role of reflexes arising in the mucosa of the respiratory passages is still to be evaluated. These reflexes and the effect of anoxia have special importance in cases of *strangulation, asphyxia or drowning.*

Clinical Types of Pulmonary Edema

While different signs have led to the recognition of various clinical pictures of pulmonary edema, *duration of the episode* allows division as follows: (1) fulminating (5 to 10 minutes); (2) acute (10 to 60 minutes) and (3) protracted (1 to 36 hours).

However, the attention of one of the writers was called several years ago to the fact that two groups deserve separation because of the different effect that treatment exerts on the clinical picture and on the final course.

Patients of the *first group*, which seems to be the most numerous, present evidence of increased blood pressure,[61] rapid circulation, increased cardiac output[57] and extreme rise in pulmonary arterial pressure.[57] This group includes cases with hypertensive heart disease; syphilitic or rheumatic heart disease with isolated aortic insufficiency; some of the cases with cerebrovascular accidents, mitral insufficiency or minor coronary episodes; and patients treated with too abundant venous infusions or transfusions. It is apparent that any method which succeeds in decreasing venous return to the right heart will be most effective in this type of edema.

Patients of the *second group*, less numerous but tending to increase, present either no change or a drop of blood pressure,[61] decreased cardiac output and a more moderate rise in pulmonary arterial pressure (some cases may even have a normal pulmonary arterial pressure). This group includes cases with massive myocardial infarct, some of the cases with

TABLE 4.—*Pharmacologic Treatment of Pulmonary Edema*

Drug	Indication	Contraindication	Mechanism of effect
Atropine	Coronary occlusion, CVA attacks	Other cases	Blocks vagus (increased heart rate helps if there is severe bradycardia)
Morphine	Hypertension, coronary occlusion, mitral stenosis	Shock, allergy, toxic gases, pregnancy, drowning, CVA attacks	Slower respiration, decreased metabolism, decreased reflexes, decreased venous return (probable), decreased peripheral resistance
Barbiturates, chloral	See above	See above	See above
Mercurial diuretics	See above	See above	Decreased venous return and venous pressure
Ouabain, Digitoxin	Hypertension, CVA attacks	Mitral stenosis. Massive myocardial infarction. Toxic gases, drowning.	Increased dynamics of both ventricles (mostly the right if the left is damaged or there is mitral obstruction)
Sympatholytics, spinal anesthesia	See above	Shock, toxic gases, drowning	Peripheral vasodilatation with shift of blood from lungs toward periphery
Aminophyllin	See above	See above	See above (moderate effect)
Antihistaminics	All cases	—	Prevention of histaminic effect on capillary wall, possible central sedation
Heparin*	All cases	—	Decreased permeability of capillary wall

* So far, only experimental pulmonary edema.

severe mitral or aortic block, some cases following inhalation of toxic gases, some cases of cerebrovascular accidents and some cases with toxic, rheumatic or bacterial myocarditis. While a reduction in venous return may be useful in these cases, it also carries with it the danger of precipitating shock.

THERAPY

The multiple etiologies and the various mechanisms, which may be involved in pulmonary edema, have led to the employment of a multiplicity of drugs and physical measures. Unfortunately, tradition on the one hand and erroneous concepts on the other have prevented, so far, a rational approach. Although little agreement exists between different groups of physicians, each group treats all cases of pulmonary edema in a similar manner.

Table 4 summarizes the various drugs; table 5, the physical or physicochemical methods of treatment.

Drug Therapy

Morphine. The empirical use of opiates is old. The value of morphine was demonstrated in various types of experimental pulmonary edema.[8, 16, 32, 63] Morphine terminates most of the mild and some of the severe clinical attacks. However, the best results are obtained in

TABLE 5.—*Physical or Physicochemical Treatment of Pulmonary Edema*

Treatment	Indication	Contraindication	Mechanism of Effect
Hot bath	Hypertension	Other cases	Vasodilation, decreased venous return
Venesection, application of tourniquets	Hypertension, mitral stenosis	Other cases	Decreased venous pressure and venous return
Oxygen inhalation	All cases	—	Decreased anoxia
Pressure respiration	Most cases	Shock	Resistance to transudation, decreased venous return
Alcohol vapor or aerosol	Most cases	Inhalation of toxic gases	Changes of surface tension, decreased foaming, decreased anoxia, mild sedation
Silicone aerosol	Inhalation of toxic gases	—	Changes of surface tension, decreased foaming, decreased anoxia

cases with hypertension, uremia or mitral stenosis. The untoward effect of morphine in cerebral accidents or lesions and in chronic cor pulmonale, may contraindicate or limit its use in such cases. The deleterious effect of morphine on the fetus may indicate the need for a cautious use of this drug in attacks occurring during pregnancy. Even in cases of coronary occlusion, large doses of morphine may favor the onset of shock.

The mechanism of action of morphine is not completely known. This drug depresses the respiratory center and decreases the suction effect of dyspnea (which in turn may decrease the edema). In pharmacologic doses, morphine causes no apparent changes of cardiovascular dynamics,[6] and the pulmonary vessels are affected only by extremely large doses.[64] Pulmonary arterial pressures of cardiac patients, studied by catheterization, decreased in 26 out of 34 cases, but increased in the other eight.[65] It is, therefore, difficult to foresee whether the effect of morphine will be beneficial. Alleviation of anxiety and interruption of harmful reflexes may be a useful action of morphine, especially in coronary patients. Vomiting may be deleterious and even dangerous. Morphine decreases the basal metabolic rate; this should decrease the work of the heart and lower the venous pressure. However, it may take some time for this effect to become apparent.

Morphine is usually administered subcutaneously, in doses of 10 to 15 mg. It may be given intravenously, as shown by one of the authors (A.A.L.) in 1928.[66] Intravenous administration is followed by more rapid effects, but causes nausea more frequently.

Atropine. Atropine was used empirically in England for a long time before any publication described its beneficial effect in pulmonary edema.[67] It is likely that the well-known "drying" effect of atropine on secretions and the results obtained in bronchial asthma (which originally was not clearly separated from other syndromes) were responsible for its being prescribed in pulmonary edema.

Atropine was found either mildly beneficial[16] or harmful[63] in intact animals and only slightly beneficial in tracheotomized animals,[50] when pulmonary edema was induced by means of epinephrine or rapid intracarotid infusion. Atropine does not improve pulmonary edema caused by ingestion of ammonium chloride[3] while it is beneficial in pulmonary edema caused by the central nervous system lesions.[3] The latter effect seems due to prevention of extreme bradycardia, one of the possible factors of pulmonary congestion. The clinical use of atropine should be limited to neurologic conditions with bradycardia and to some cases of coronary occlusion, also presenting bradycardia. In the other cases, tachycardia, caused by atropine, and vagal inhibition in general may be detrimental. Bronchodilation caused by atropine has been considered either harmful[68] or useful[69] according to different theories. For the above reasons, *Demerol*, a drug with both an atropine-like and a morphine-like action, should not be preferred to morphine, except in cases with a definite indication for the use of atropine.

Barbiturates-Chloral. Barbiturates and chloral hydrate have been shown to be of value in experimental pulmonary edema.[16] Their intravenous administration in man was attempted long ago[66] and their value in several cases of pulmonary edema has been shown since 1930.[3, 74] However, these drugs may be ineffective and, in certain cases, one cannot escape the impression that the deep sedation produced by them hastens the patient's demise. Venous return is decreased by chloral and barbiturates, and it is only logical to avoid use of these drugs in patients of the second group, those in danger of shock.

Aminophyllin. This drug is a mild vasodilator, a bronchodilator, and a stimulant of the respiratory center. The first action is useful though inadequate, the second is of doubtful utility (see atropine) and the third is definitely detrimental.[16] For these reasons, aminophyllin should not be used in the emergency treatment of the attack. The routine use of aminophyllin, practiced in certain hospitals, cannot be recommended.

Papaverine. Intravenous injection of papaverine in association with other drugs has been advocated by one of the authors (A.A.L.) since 1930.[3, 74] Papaverine is a smooth muscle

relaxant and a vasodilator. Its usual dose is 10 mg. intravenously. Possible objections to its use are: (1) if the patient belongs to group 1 (high output), papaverine is too mild a vasodilator to be effective; (2) if the patient belongs to group 2 (low output), even a moderate decrease of venous return can be dangerous.

Amyl Nitrite. This drug is used empirically by inhalation in some hospitals. It is very probable that its powerful vasodilator effect may be useful in certain hypertensive patients, in spite of its extremely short duration of action. However, since this drug may dilate the pulmonary vessels, the authors do not recommend it, even in cases of group 1. As far as patients of group 2 are concerned, the use of amyl nitrite presents the same dangers as that of other vasodilators.

Mercurial Diuretics. Mercurial diuretics are injected intravenously in pulmonary edema in many hospitals. Empirical use of these agents undoubtedly rested on the hope of rapid dehydration of the patient obtained through promotion of diuresis. This action, however, would hardly be adequate and timely for improving the circulation during the attack. Another property of the mercurials was subsequently described, when cardiac catheterization revealed that *Novurit* causes an important drop of pressure in the right atrium and ventricle within 20 to 30 minutes.[70] This drop in pressure is still unexplained and may be due to venous constriction decreasing venous return. This effect should be considered useful in patients of group 1 (high output) but unwanted and possibly dangerous in patients of group 2 (low output).

Sympatholytics. Drugs inhibiting or preventing stimulation of the sympathetic system have been considered helpful following demonstration that bilateral stellectomy was useful in preventing pulmonary edema in man[103] as well as in experimental animals,[48, 18] and also that spinal anesthesia produced similar beneficial effects in man.[76] In animals, sympatholytic drugs have been shown to favorably affect the course of the edema caused by intravenous epinephrine,[17, 77] rapid intracarotid infusion of saline,[50] ingestion of ammonium chloride,[32, 33] pulmonary embolism[72] or intracisternal injection of fibrin.[44, 79] Scanty clinical reports[75, 78] seem to indicate beneficial effect in man. Like all hypotensive drugs, sympatholytics (Dibenamine, Hydergine) and ganglionic blocking agents (Arfonad, tetraethylammonium chloride) may induce shock in patients of group 2. Disadvantages of these drugs are their lasting action and the difficulty of counteracting their effect, whenever this proves to be harmful.

Digitalis Glycosides-Ouabain. According to the theory of left ventricular failure, attacks of pulmonary edema are caused by an acute weakening of the left ventricle. Therefore, intravenous administration of drugs stimulating the myocardium, like strophanthin (or ouabain), was advocated since the early twenties[89] in the emergency treatment of these attacks. More recently, intravenous Digitoxin or lanatoside C were substituted for strophanthin and in many hospitals intravenous Digitoxin has become part of the routine therapy. A recent study[112] advocates small doses of ouabain (0.05 to 0.2 mg.) in the treatment of cardiogenic shock with pulmonary edema.

This therapeutic concept presupposes: (1) that the left ventricle can still be stimulated although this may not be possible when the ventricular wall is damaged by recent coronary occlusion or prolonged and severe coronary insufficiency and (2), that the right ventricle is not unduly stimulated by the drug, so that no further rise of pulmonary arterial pressure will take place. It is interesting to note that, according to many authors, digitalis glycosides have their greatest effect whenever the myocardium is functionally under stress while not structurally damaged. This seems to apply more to the right than the left ventricle during an attack of pulmonary edema because the right ventricle is under stress on account of acute pulmonary hypertension and is seldom damaged to the extent of the left.

Digitalis glycosides rapidly lower venous pressure; however, this effect is mainly due to improved function of the myocardium. Therefore, and purely on theoretic grounds, digitalis and ouabain should be useful *after* the attack in hypertensive patients even though

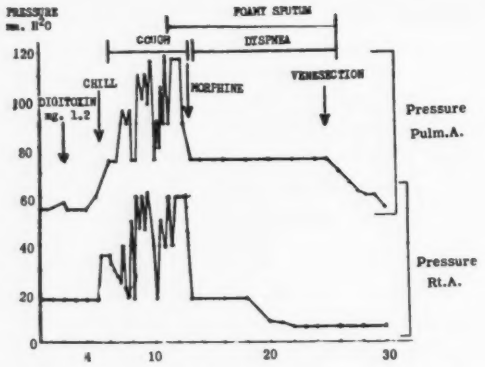

FIG. 3. Pressure of the pulmonary artery and right atrium during cardiac catheterization in a patient with mitral stenosis. Injection of 1.2 mg. of Digitoxin via the catheter was followed by pulmonary edema. Morphine and venesection terminated the attack (from Lenègre and Scébat[57]).

these drugs might be detrimental *during* the attack in cases of myocardial infarction.*

A special case should be made for patients with mitral stenosis. In these patients, the high pressure of the pulmonary capillaries is caused by high right ventricular output in the presence of mitral obstruction.† Rapid digitalization can increase the severity of the edema, if performed during an attack, and may even precipitate pulmonary edema by increasing right ventricular output while the outflow from the lungs is impeded by the mitral block.[111] A striking demonstration is given (fig. 3). Injection of 1.2 mg. of Digitoxin in a patient with mitral stenosis during catheterization was rapidly followed by pulmonary hypertension and pulmonary edema. Morphine and venesection lowered pulmonary pressure and this was followed by cessation of foaming.

Antihistaminics. The concept that liberation of histamine was the final event preceding edema of the lung has been advanced by one of the authors (A.A.L.) and co-workers since 1930. This concept seemed to be corroborated by subsequent studies[60] but is still far from being conclusively demonstrated.

Antihistaminics (*Phenergan*) seemed to give good results in experimental[81, 82] and clinical[8] pulmonary edema. However, the former effect has not been confirmed.[84] Depression of the central nervous system caused by these synthetic drugs may contribute to the results obtained.

If the main action of the antihistaminics is at the site of liberation of histamin, it is likely to be exerted within the walls of the pulmonary capillaries (fig. 4).

Heparin. Heparin was found beneficial in experimental pulmonary edema.[50, 80] Clinical reports are still unavailable. As this drug is known to decrease capillary permeability and the other anticoagulants do not share its beneficial action in pulmonary edema,[50] the effect of heparin is probably due to local action on the capillary wall.

Corticotropin (ACTH). Corticotropin has been found beneficial in acute pulmonary edema of rabbits.[53, 80] Considering that its effect was obtained after four days of treatment, this drug might be considered *in the*

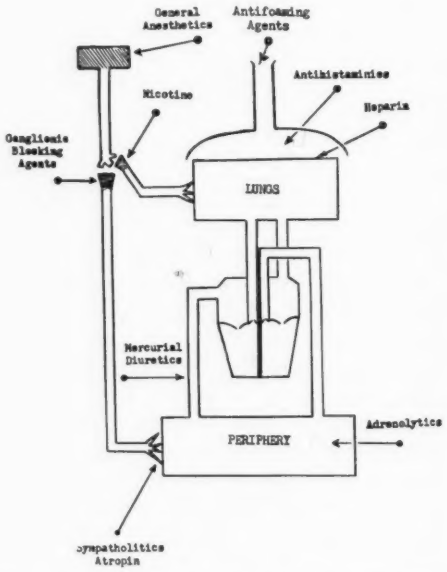

FIG. 4. Site of action of the most used drugs

* Experiments testing intravenous digitalis in pulmonary edema are being done in this laboratory.

† In certain cases, vasoconstriction of the pulmonary arterioles prevents an excessive rise of pressure in the capillaries of the lungs.

prevention of the clinical attacks, but not in their therapy.

Physical, Physicochemical and Surgical Treatment of Pulmonary Edema

Several physical or physicochemical procedures have been used. Some are effective and should be considered in certain cases.

A *hot bath* (*Sitzbath*) has been used empirically and may be of help by causing peripheral vasodilatation. It is particularly indicated in patients with hypertension or aortic insufficiency.

Venesection or application of tourniquets is an old procedure. It is extremely effective in patients with arterial hypertension or aortic insufficiency and in certain cases of mitral stenosis with high venous pressure. As the main result is decreased venous return, venesection is contraindicated in patients of group 2 because it may induce shock. The general procedure is withdrawal of 500 to 600 cc. of blood from an antecubital vein by means of a 15 gage needle or after cutting the vein with a scalpel. If the *tourniquet* procedure is used, these bindings are applied to the four limbs with a moderate pressure; each is released and reapplied every 20 to 30 minutes in order to avoid venous thrombosis.

Oxygen was used at first only in cases with pronounced cyanosis. As anoxia may occur in pulmonary edema either as a primary or as a secondary factor, the use of oxygen is rational. Moreover, clinical improvement follows its use in certain cases. It is unfortunate that foam in the bronchioles prevents oxygen from reaching many of the alveoli. Oxygen is usually administered in the form of 100 per cent oxygen with a humidifier in order to prevent drying of the mucosae. As oxygen in high concentrations is irritant, its administration should be interrupted by periods of normal air breathing.

Pressure respiration has been advocated in the treatment of pulmonary edema. The theoretic basis of this method is that the increased pressure in the broncho-alveolar system counteracts the high pulmonary capillary pressure and decreases transudation. Following animal experimentation, Barach and associates[85] suggested breathing against a positive pressure of 3 to 6 cm. water. This procedure produced useful results in several clinical cases and seemed particularly indicated in pulmonary edema due to gas poisoning.[86]

It has been shown that positive pressure respiration, by increasing intrapleural pressure, decreases venous return.[104] This procedure, which may be useful in patients of *group 1*, presents some danger in patients of *group 2*, where impending shock might be precipitated.*

Spinal anesthesia was tried by Sarnoff and Farr[76] with encouraging results in clinical cases of protracted pulmonary edema which were refractory to other therapy. The intensive vasodilatation which follows spinal anesthesia decreases venous return to the right heart and lowers pulmonary arterial pressure. It is likely that the mechanism of action and the contraindications of this technic are similar to those of sympatholytic drugs (page 123).

Stellate block has proved useful in experimental pulmonary edema, when tried by a co-worker of the author.[48] Clinical use of this method was made in 1952 by Pierach and Stotz.[103] They blocked the right stellate ganglion with procaine in eight clinical cases of pulmonary edema with hypertensive, coronary or rheumatic heart disease. Excellent results were reported. The authors state that only the right ganglion should be blocked while block of the left would increase pulmonary congestion. Explanation of the mechanism of action is only tentative.

Antifoaming Therapy

Pulmonary edema, whatever the initial cause, starts a vicious circle of events which tends to prolong the attack. This cycle is based

* While positive pressure obtained by an expiration valve definitely decreases venous return, positive pressure respiration with modern apparatus seems to increase intra-alveolar pressure only for an extremely brief time. If this is confirmed, the latter method might be applied to any case of pulmonary edema without danger.

on high pulmonary capillary pressure, transudation and accumulation of fluid in the alveoli, foaming and local anoxia, which in turn leads to more transudation, more foaming and more anoxia. While any procedure tending to lower pulmonary capillary pressure is undoubtedly the most effective in patients of *group 1*, these procedures are either poorly effective or acually dangerous in patients of *group 2*.

Since 1950 we have tried a new approach, that of attempting to break the cycle by acting on the foaming process itself. It was shown long ago[87] that large amounts of fluid may be present in the air passages with little danger to life; as soon as the surface tension of the fluid reaches a critical point, foaming starts. This leads to extremely severe effects, partly through the enormous increase in volume (foam) and partly through modification of the normal alveolar function which is based upon surface tension effects between humid alveolar surface and air.[88]

Since impairment of the normal gas exchanges of the lungs is followed by anoxia which in turn causes increased permeability of the capillaries,[69] the foaming process in itself may be responsible for the continuation of the attack and may be a cause of death. If a modification of the surface tension of the foam is brought about, the bubbles burst and the fluid composing the thin separating layers then occupies a much smaller volume.

Antifoaming or *defoaming agents* (ether, octyl alcohol, capryl alcohol and ethyl alcohol) were tested by one of us in the form of vapors or aerosols in four different types of experimental pulmonary edema.[90, 91] While the use of long chain alcohols did not seem to improve the outcome, ether had a mildly beneficial action and ethyl alcohol (ethanol) produced excellent results. The inhalation of oxygen with a high concentration of *ethyl alcohol vapor* was followed by a decreased mortality, a lower lung-body index and the easy expectoration of fluid. The systemic effect of alcohol was slight, both on account of its being only a mild sedative and vasodilator, and because of poor absorption. This was shown by the observation that beneficial effects of alcohol by other routes were obtained only when administered in doses which induced deep anesthesia.[91]

Experimental studies have also been made by others with *silicone* in ether[92] or in water;[93, 94] both were found beneficial. We have recently compared several antifoaming agents including silicone mixtures.[94] Three agents were definitely beneficial: 10 per cent silicone in water, freon and ethyl alcohol. Since freon may present some dangers if administered for long periods, only alcohol and silicone were considered for clinical use. While alcohol yields superior results in experimental pulmonary edema induced by adrenalin, it has a moderately irritant effect on the bronchial mucosa. This should favor the use of aerosol solutions of *silicone* in forms of pulmonary edema caused by lung irritants (chlorine, etc.). Experiments in this direction seem to confirm this viewpoint.[95, 108, 114] The effectiveness of silicone aerosol tends to support the opinion that the utility of alcohol vapor is not due to systemic effect, but rather to its effect on surface tension of the foam.

Several studies with antifoaming agents in clinical cases of pulmonary edema have been reported. At first, the tolerance for alcohol and the best method of administration were studied in normal volunteers as well as in cardiac patients without pulmonary edema.[96, 99] Two methods which gave excellent results are: (1) Use of a face mask and a 20 to 30 per cent alcohol solution. This technic is especially suited for comatose patients. (2) Use of a nasal catheter and a 95 per cent alcohol solution. This method is to be preferred in conscious patients.

In both methods, the alcohol is placed in the usual humidifier bottle, connected to an oxygen tank. The oxygen flow is kept at 2 to 3 liters per minute for the first few minutes. Then, when the patient's mucosae become adapted to the irritant gas (local anesthesia?), the flow rate is gradually stepped up until, after 10 to 12 minutes, it reaches 9 or 10 liters per minute, and is maintained at such level.*

* It should be emphasized that prolonged alcohol vapor treatment should be done only by alternating periods of inhalation (30 to 40 minutes) and periods of rest (10 to 15 minutes) during which the patient is

By means of this technic, alcohol vapor was administered to 14 patients during 17 severe or extremely severe attacks of pulmonary edema. In 14 of the attacks, previous conventional therapy had failed; in the other three, alcohol was the only therapy used. When oxygen-alcohol vapor was administered, the results were dramatically favorable in 10 of the attacks and definitely helpful in the other 4.

It was noted that patients with severe attacks responded most dramatically and that those with attacks of shorter duration had a more rapid recovery following alcohol vapor inhalation. Usually, subjective relief preceded objective improvement, so that the patient felt completely recovered even though some chest rales were still audible.

The beneficial effects of alcohol vapor were also noted by Goldmann and Primiano in one obstetrical case,[97] by Gootnick and co-workers[98] in two cases (one of them in shock) and by Weyl in seven surgical cases.[102] A further report summarized the results of alcohol therapy in 50 attacks[99] (table 6).

Another method was tried by Sadove,[109] 12 per cent alcohol aerosol by face mask. His results were equally good.

The following abridged case reports illustrate the efficacy of this method of treatment.

Case 1. A 50 year old white female with *hypertensive cardiovascular disease* was semicomatose and unimproved one hour and a half following the onset of acute pulmonary edema of 4 plus severity. Oxygen bubbling through 95 per cent alcohol was administered via nasal catheter and dramatic improvement ensued. Forty-five minutes after therapy was begun, improvement was 4 plus subjectively and objectively. Therapy was discontinued after two hours and 15 minutes. No other treatment for acute pulmonary edema was given before or after the inhalation. The patient was later discharged to the Cardiac Clinic.

Case 2. A 65 year old, white female with acute pulmonary edema of 3 plus severity and of three hours duration was admitted to the hospital for treatment. Oxygen by mask for 30 minutes failed to induce improvement and no other treatment had been given. Thirty minutes after the inhalation of oxygen-alcohol vapor via nasal catheter was started, improvement was marked subjectively and objectively. Toleration of the vapor was good. After 45 minutes, treatment was discontinued. A diagnosis of *hypertensive cardiovascular disease*, class III, with left ventricular hypertrophy, was established. After convalescence, the patient was discharged to the Cardiac Clinic.

Case 3. A 65 year old white female with *coronary heart disease* and *calcific aortic stenosis* suffered from a *posterior myocardial infarction* and developed *shock* and acute pulmonary edema of 4 plus severity. Morphine sulfate 15 mg., atropine sulfate 1.2 mg. and Desoxyn 10 mg., were administered intravenously. Notwithstanding these measures, her blood pressure dropped to 70/60 mm. Hg. Ninety minutes later, the patient was considered to be agonal and oxygen-alcohol vapor was administered by mask. Toleration was good. Improvement was gradual and progressive, being 4 plus subjectively and objectively at the end of six and one half hours. After eight and one half hours, alcohol therapy was discontinued. The patient was discharged four weeks later.

Case 4.[102] A 61 year old patient was suffering from pyloric obstruction and was scheduled for

TABLE 6.—*Results of Alcohol-Oxygen Vapor Therapy in Clinical Cases of Pulmonary Edema**

Mode of Therapy	Attacks Treated	Degree of Severity	Degree of Improvement
Alcohol-oxygen vapor only	3	++++	++++
	9	+++	+++
	2	++	++
	Total 14		
A.O.V. given after failure of other procedures	11	++++	++++
	5	+++	+++
	1	++	++
	Total 17		
Possible contributory action of other procedures	3	++++	++++
	6	+++	+++
	Total 9		
All methods	17	++++	++++
	20	+++	+++
	3	++	++
	Total 40		

* From Goldmann and Luisada[99]

Severity of attacks graded as follows: ++++ very severe, +++ severe, ++ moderate.

Improvement graded as follows: ++++ complete or almost complete, +++ good, ++ fair.

breathing air or oxygen. This prevents excessive absorption of alcohol which might lead to unwanted systemic effects.

TABLE 7.—*Treatment of Pulmonary Edema following Failure to Respond to Antifoaming Therapy*

	Arterial Pressure	Venous Pressure	Consciousness	Pulse	Drug	Physical or Surgical Procedures
(1) Cases with myocardial infarct	Above 100 (above 120 in hypertensive cases)	Normal or slightly elevated	Normal	Rapid and regular	Morphine 15 mg., mercuhydrin 1 cc. i.v.	—
	Above 100 (above 120 in hypertensive cases)	Normal or elevated	Normal	Slow and regular	Morphine 15 mg., atropine 0.5 mg., mercuhydrin 1 cc. i.v.	—
	Below 100 (100–120 in hypertensive patients)	Severely elevated	Lost	Rapid, slow, or irregular	Morphine 10 mg or Demerol 50 mg.	If i.v. fluids are necessary, use extreme caution (slow rate, moderate amount). If norepinephrine is given, use moderate doses.
(2) Cases with cardiovascular accidents	High	Normal	Lost	Slow	Atropine 0.5 mg. (chloral 1 Gm. ?), mercuhydrin 2 cc. i.v.	Pressure respiration. Venesection. No i.v. fluid. Spinal anesthesia. Procaine block of right stellate ganglion.
	Low	High	Lost	Rapid		Pressure respiration
(3) Rheumatic heart disease (mitral stenosis or complex valvular lesions; possible carditis)	Above 100	Slightly elevated	Normal	Rapid and irregular	Morphine 15 mg., mercuhydrin 1 cc. i.v.	Pressure respiration. Venesection
	Below 100	Severely elevated	Normal or semi-comatose	Rapid and irregular	Morphine 10 mg., mercuhydrin 2 cc. i.v.	Pressure respiration
(4) Hypertensive heart disease or syphilitic heart disease with aortic insufficiency	Above 200	Normal or slightly elevated	Present	Rapid	Morphine 15 mg., mercuhydrin 2 cc. i.v. (chloral 1 Gm.?)	Pressure respiration. Venesection
	Below 200	High	Present	Rapid	Morphine 10 mg.	Pressure respiration. Spinal anesthesia. Procaine block of right stellate ganglion
(5) Inhalation of toxic gases or bronchial obstruction					Morphine 5 mg. or Demerol 25 mg.	Pressure respiration

astric resection. Past history revealed exertional lyspnea and bilateral intermittent claudication fter walking two blocks. An electrocardiogram howed low voltage and diphasic T in aV_L. Induc- ion of anesthesia and intubation were uneventful. Balanced anesthesia with circle absorption tech- ique was used and respiration was assisted. Pulse nd blood pressure were satisfactory (blood pres- ure, 140/80; pulse, 100) and color was good. One int of blood was given in one and one-half hours. After the peritoneum was closed, only 50 per cent itrous oxide oxygen was administered. At the end f the three-hour operation, cyanosis was noted. The pulse was 140; blood pressure 100/60. Sudden ppearance of foam from the mouth then occurred nd gurgling and bubbling sounds were heard. Im- mediate inhalation of oxygen-alcohol vapor was instituted by mask and, within 20 minutes, the pulmonary edema had subsided, the chest sounded clear, the color was pink, and the patient seemed improved. An electrocardiogram showed changes in aV_L, T, and V_4 through V_6. Subsequent tracings showed definite evidence of an *acute anterior wall infarct.* The patient made an uneventful recovery and left the hospital six weeks later in good condition.

Case 5.[97] A 43 year old Negro woman was admitted to the hospital because of *hypertension complicating pregnancy.* Hypertension had been noted during two earlier pregnancies; however, no interim examinations had been performed. Physical examination revealed an obese woman with blood pressure of 230/140, pulse 84, temperature 98.6 F., and respiration 20. The size of the uterus was consistent with a nine month gestation.

While lying supine following the examination, the patient became severely dyspneic and cyanotic, and developed acute pulmonary edema of the greatest severity, with continuous emission of copious amounts of pink, frothy fluid from the nose and mouth. The patient's head was elevated and positive pressure oxygen by mask was instituted. Successively, morphine sulfate 30 mg., aminophyllin 0.5 Gm., atropine sulfate 0.5 mg., sodium amytal 0.5 Gm. and Digalen (1 cat unit) were administered intravenously within 15 minutes from the onset of the attack. Forty minutes after these measures were completed, the patient was delirious and frothy sputum was still being emitted in copious quantities from the mouth.

Administration of alcohol vapor was then started via face mask. It was necessary to remove the mask frequently to permit removal of collected foam. Improvement was prompt, dramatic and progressive. Within 15 minutes, the foam became more liquid in character and expectoration was more effective. At the end of 30 minutes, the patient was able to sit up and speak clearly, although with some effort. Bubbling sounds and crepitant pulmonary rales on auscultation were now markedly reduced. At this point, alcohol vapor was given and treatment was discontinued. Approximately seven hours later, the patient spontaneously delivered a female infant who required tracheal catheterization and oxygen.

Protracted pulmonary edema often starts suddenly but has a protracted course and is less likely to be a crucial issue for the prognosis. Ten such cases, all of them in poor or terminal state, were submitted to alcohol vapor therapy, in spite of the fact that none was considered likely to survive.[99] Seven cases improved but the improvement was slower and less marked than in the acute attacks. It was good in three, moderate in two and minimal in two. The following case is an example.

Case 6. A 65 year old white male with *coronary heart disease* and *congestive failure* gradually and progressively developed pulmonary edema of 3 plus severity (over a period of 15 hours). Oxygen via nasal tube, morphine sulfate 15 mg. hypodermically, aminophyllin 0.25 Gm. and 3 units of Digalen intravenously, were given without noticeable improvement. Oxygen-alcohol vapor was started via nasal catheter and improvement was 3 plus objectively 20 minutes later. After 40 minutes of alcohol vapor treatment, improvement was so well established that this therapy was discontinued. The patient died suddenly on the following morning. Autopsy revealed a *recent anteroseptal infarction,* marked *left ventricular hypertrophy* and *absence of froth* in the tracheo-bronchial tree.

Following these reports, alcohol vapor treatment of pulmonary edema was instituted in various hospitals. It is unfortunate that, although the results are usually described as good, no other accurate clinical reports have been published.

The good results of another antifoaming agent, *2-ethyl-hexanol,* was stressed by Reich and associates,[100, 101] following its use in 14 unselected cases. One-half of the patients showed a good response. Other antifoaming agents are being tested by various investigators including Sadove.[109]

Management

Treatment of the Attack

At present, the directions for management of the attack are still tentative (table 7).

Further studies on the mechanism of action of the various drugs and physical procedures used in the different clinical types of pulmonary edema are necessary.

Antifoaming therapy is compatible with any other drug or physical treatment. Therefore, it is the viewpoint of the authors that all cases of pulmonary edema should be immediately treated with an antifoaming agent. In cases of pulmonary edema due to inhalation of toxic gases, silicone aerosol may prove to be the agent of choice. While the patient is undergoing inhalation treatment, a thorough examination of the causes leading to the attack should be made and their effects on the patient noted (pulse, blood pressure, electrocardiogram). After this routine examination, which may take from 20 to 30 minutes, and if the attack has not subsided, other procedures should be instituted.

Cases of pulmonary edema, associated with hypertension or aortic insufficiency, stenosis or coarctation, should receive 15 mg. of *morphine* and may also receive an intravenous injection of a *mercurial diuretic*. *Sympatholytic drugs* may be given but other hypotensive agents (such as nitroglycerine, papaverine), having a shorter action, may be preferred.

Cases with myocardial infarct and blood pressure above 100 or above 120, if there was hypertension prior to the attack, should also receive 15 mg. of *morphine*; 0.5 mg. of *atropine* may be administered if there is marked bradycardia. *Mercurial diuretics* may be given, but in small dose (1 cc. intravenously). If the blood pressure drops below 100 mm. Hg, the dose of morphine should be not more than 10 mg., and no mercurial may be given. The same rationale applies to cases of rheumatic heart disease and mitral stenosis.

Patients with cerebrovascular accidents should *not* receive morphine. They may be given *atropine*, *mercurials* and, possibly, *chloral hydrate* by rectum or intravenously.

Morphine should be given only in small doses (5 mg.) to patients who have inhaled toxic gases.

Spinal anesthesia or *right stellate block* should be used only in cases of cerebrovascular accicents or hypertensive heart disease with protracted edema, which is refractory to treatment, and then only if blood pressure is high.

Venesection occasionally may be a life-saving procedure. It should be employed only in cases of hypertension, cerebrovascular accidents, mitral stenosis or aortic insufficiency having high venous pressure or visible venous engorgement. Its use in other cases is more questionable, even in the presence of venous engorgement. As an example, in patients with myocardial infarct and systemic venous congestion, venesection may precipitate shock.

Pressure respiration has, in general, a favorable effect in pulmonary edema. However patients with cerebrovascular accidents and depression of the respiratory center may respond poorly to this treatment.

Prophylaxis

It should be kept in mind that *transfusions of blood* and *infusions of plasma or saline strongly favor pulmonary edema*. Failure to consider this fact is responsible for many episodes of edema in medical and surgical wards. Moderation and wisdom in the administration of intravenous fluids may prevent many attacks, not only in cases with coronary or rheumatic heart diseases or anemia, but also in patients whose myocardium is less efficient because of anesthesia, surgical intervention or infection.

Prevention of pulmonary edema in *hypertensive patients* can be obtained in two ways: (1) by decreasing the load placed upon the left ventricle (salt poor diet, hypotensive drugs, sympathectomy, sedation); or (2), by stimulating the myocardium (digitalis glycosides). Both methods are extensively used. This may account for the impression that occurrence of pulmonary edema in these patients is less frequent than formerly.

Prevention of pulmonary edema in patients with *coronary* or *cerebrovascular diseases* is more difficult: prevention of the arteriosclerotic process would be the answer. Central sedation, especially at night, may prolong the life of these patients.

Prevention of pulmonary edema in *rheumatic heart disease* is based on avoidance of excessive physical work, on salt restriction,

use of diuretics and digitalization. Mitral valvotomy is effective in preventing attacks of pulmonary edema of patients with mitral block. In *acute rheumatic fever*, adrenocortical extracts are the best treatment, whenever the myocardium is severely damaged. The same treatment may be lifesaving in rheumatic heart disease with silent rheumatic carditis.

Most of the other forms of pulmonary edema are caused by unpredictable and often unavoidable events. The incidence of pulmonary edema in these cases will be reduced following improvement of working conditions (decreased exposure to toxic material), improvement of medical technics (slow removal of serosal fluids, moderation in the administration of intravenous fluids, rational anesthesia) and improved therapy of infections, including those involving the heart or the nervous system.

Summary

Acute edema of the lungs is the infiltration of serum into the interstitial pulmonary tissue, followed by exudation into the alveolar cavities, frothing and expectoration of foam.

Acute pulmonary edema is encountered in a great variety of conditions including cardiovascular, renal, cerebral and pulmonary diseases, trauma to the skull or the chest, infections and shock.

Pulmonary edema may be fulminating, acute or protracted. Two clinical types can be recognized, that associated with a full pulse, a high blood pressure and a high output (*group 1*), and that associated with severe blood pressure drop, low output and tendency toward shock (*group 2*).

Experimental pulmonary edema can be produced by a great variety of methods. These range from damage to the heart or brain to ventricular strain; from trauma to the skull or chest to pulmonary embolization; from overload of the circulation to inhalation of toxic gases or administration of poisons.

The mechanism of production of pulmonary edema is still somewhat obscure. Three main factors seem of paramount importance: high pressure in the pulmonary capillaries, increased permeability of these capillaries, and decreased osmotic pressure of the blood. While strong sympathetic stimulation is one of the most common factors leading to displacement of a large mass of blood from the periphery to the lungs, the roles played by vascular phenomena in the lungs, secretion of endocrine glands and locally elaborated humoral agents are still under discussion.

Special aspects of the treatment of pulmonary edema in mitral stenosis, in massive myocardial infarct and in exposure to toxic gases are discussed.

Therapy of pulmonary edema is based on the use of drugs and physicochemical means. Among the most successful drugs are morphine, mercurial diuretics and sympatholytics, while oxygen therapy, pressure respiration and venesection may also be useful. Most of the above drugs and physical procedures tend to decrease venous return and cardiac output; therefore, while helpful in patients of *group 1*, they may induce shock in patients of *group 2*.

Digitalization during the attack is considered of questionable value, particularly in cases of myocardial infarct, mitral stenosis or exposure to toxic gases. It may be useful in the prevention of the attacks.

Antifoaming therapy is a purely symptomatic treatment which tends to break a self-perpetuating cycle by modifying the surface tension of the froth, thus reducing its volume. This procedure has been shown to be of definite value and should be used routinely as the first remedy, even preliminary to a brief study of the case. Drug therapy and other physical measures should be employed later, after an evaluation of the clinical picture, and, especially, if antifoaming therapy fails to terminate the attack.

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ABSTRACTS

BACTERIAL ENDOCARDITIS

Fisher, A. M., Wagner, H. N. and Ross, R. S.: Staphylococcal Endocarditis. Arch. Int. Med. **95:** 427 (March), 1955.

The high incidence of antibiotic-resistant strains represents one of the major problems in the therapy of staphylococcal infections at the present time. Some of the diagnostic criteria for staphylococcal endocarditis are evaluated and discussed.

Data have been reviewed on 38 cases of staphylococcal endocarditis. Thirteen of these were seen during the five-year period from 1949 through 1953. The incidence of penicillin-resistance in this last group was 42 per cent. The survival rate was 54 per cent.

Recovery showed no definite correlation with sensitivity of the staphylococcus to penicillin. It seemed dependent, however, on the administration of massive doses of penicillin with erythromycin or other antibiotics, irrespective of the results of in vitro tests for penicillin sensitivity.

BERNSTEIN

Rhoads, P. S., Sibley, J. R. and Billings, C. E.: Bacteremia following Tonsillectomy. J.A.M.A. **157:** 877 (March 12), 1955.

The clinical investigation was undertaken to throw light on the questions of (1) the presence of a transient bacteremia after tonsillectomy and its prevention by preoperative treatment with penicillin and other antibiotics, (2) the amount of information regarding bacterial content of the deeper lymphoid tissue of the tonsils given by cultures from the surface of the throat and (3) how antibiotic therapy affects the bacteria in the deeper structures of the tonsils. One hundred thirty-eight patients were studied. The control group of 68 patients had no preoperative antibiotic therapy. Blood cultures were positive in 20.3 per cent of this group. Bacteremia was reduced to 5.9 per cent in a group of 20 subjects who received penicillin in a daily dose of 600,000 to 800,000 units intramuscularly for 4 to 10 days prior to tonsillectomy. The incidence of bacteremia, in 29 patients who received 600,000 to 800,000 doses (half this dose for children) procaine penicillin 12 to 18 hours and 1 hour prior to tonsillectomy or in a small group (7) of patients receiving 900,000 to 1,200,000 units orally daily for 5 to 7 days prior to operation, was not reduced below that of the control group. In the control series of 68 patients who had no antibiotic treatment β-hemolytic streptococci were present in 57.4 per cent of the cultures of the excised tonsils, although these micro-organisms were found in only 28.26 per cent of throat cultures taken just before the operation. Among the patients, receiving penicillin in single doses only the day before and the day of tonsillectomy, 31.03 per cent had β-hemolytic streptococci in the excised tonsils, although these micro-organisms were not present in the throat cultures taken just before tonsillectomy. β-hemolytic streptococci were found only once in the cultures from the excised tonsils of persons receiving penicillin intramuscularly each day for 4 to 10 days prior to tonsillectomy. Most of the gram positive micro-organisms except micrococci and *Gaffkya tetragenus* were greatly reduced in number by penicillin administered intramuscularly but gram negative micro-organisms as *Klebsiella pneumoniae*, *Aerobacter aerogenes* and *Escherichia coli* were found in increased number in cultures from the throats and excised tonsils of these subjects. The need for several days of preoperative treatment with penicillin to prevent post-tonsillectomy bacteremia (especially streptococcic) is obvious.

KITCHELL

CONGENITAL ANOMALIES

Landry, S. F., Jr. and Salatich, J. S.: Anomalous Pulmonary Arteries. Arch. Surg. **70:** 411 (March), 1955.

The authors report a case of anomalous pulmonary arteries supplying the right and left lower lobes, and described two roentgenologic aids in the preoperative diagnosis of this condition. They pointed out that a routine x-ray of the chest may show the presence of long branching lines (the anomalous arteries) directed toward the diaphragm, while planography invariably demonstrates the anomalous vessels. Other diagnostic means are directed toward the recognition of the dense sequestrated lung, a congenital defect frequently associated with anomalous pulmonary arteries. A round or triangular mass in the lower lobe, a density having a finger-like projection directed downward and medially, and a filling defect seen in bronchography suggest the presence of this condition.

ABRAMSON

Vernant, P., Nouaille, J., Schweisguth, O., Labesse, J., Bouchard, F., Mathey, J., Binet, J. P. and Oustrières, G. O.: Patent Ductus with Pulmonary Hypertension without Reversal of Shunt. Arch. mal. coeur. **48:** 277 (March), 1955.

The authors report operative results of 11 children, 11 months to 10 years old, with a patent ductus arteriosus and pulmonary hypertension of more than 15 mm. Hg. Preoperative catheterization studies performed on all revealed the direction of the shunt to be entirely or predominantly from left to right. One case died during surgery from hemorrhage and subsequent cardiac arrest. Seven cases are classified as healed, two (with concomitant aortic stenosis) as improved, and one (with a crossed shunt) as a failure.

Improvement in the seven cases was striking and consisted in resumption of growth, disappearance of the typical murmur and reduction of heart size and pulmonary hypervascularity. The electrocardiogram usually showed a transitory aggravation of a left heart strain pattern, immediately following surgery. Hemodynamic studies during surgery revealed an instantaneous drop of the pulmonary hypertension on clamping or ligation of the duct, elevation of the diastolic aortic pressure and reduction of the hypertension in the left atrium. In five cases, permanent lowering of the pulmonary arterial pressure and normalization of pulmonary arterial wedge pressure could be demonstrated by postoperative catheterization. According to the authors, in a patent ductus associated with pulmonary hypertension, surgery is urgent when the pulmonary arterial pressure is lower than the systemic pressure. When the two pressures are equal, the indication for surgery is questionable. It is definitely dangerous when pulmonary hypertension exceeds the aortic pressure. The pathogenesis of this hypertension is discussed and its complexity pointed out. It would appear that a significant mitral regurgitation, consequent to increment of the amount of blood returning to the left heart, may play a role in addition to pulmonary vascular alterations.

PICK

Rosahn, P. D.: Endocardial Fibroelastosis: Old and New Concepts. Bull. N. Y. Acad. Med. **31:** 453 (June), 1955.

A well written review of endocardial fibroelastosis is presented with detailed reports of three cases. The condition thought to be a congenital disease of unknown etiology is seen not infrequently and has no sex or racial predilection. It occurs usually in infants under 1 year of age, although it has been seen in older children. Pathologically, there is a diffuse thickening of the mural endocardium associated with myocardial hypertrophy. There may be associated valvular defects or anomalies in the great vessels. Clinically the disease is present in two ways. There is the acute form in which respiratory difficulty ensues, weight loss and cardiomegaly occur and cyanosis appears as a terminal event, usually within weeks of onset. The chronic form is a slower process occurring with frequent remissions and exacerbations lasting for about six months until death occurs. On examination, the hearts are hypertrophied, the endothelium is sclerosed and thickened, porcelain white in color. The left side is more frequently involved. Microscopically, there is thickening of the endothelium with preponderance of elastic fibers, edema and a basophilic ground substance are present in the outermost layer of the endothelium. A lengthy discussion of the various theories of the etiology is presented. None has been proven, but various authors have thought maternal infection, mechanical factors anoxia, abnormal development and genetic factors are involved alone or in combination.

HARVEY

Nisbet, N. W.: Congenital Arteriovenous Fistula in the Extremities. Brit. J. Surg. **41:** 658 (May), 1954.

The author discusses the possibility of a congenital arteriovenous fistula in the tibia which causes a giant limb and presents a case report of this type of lesion. The patient suffered from repeated trophic ulcers of the foot. Operation was performed and a large branch of the popliteal artery was ligated. During the next 12 years, the patient was without complaints except for occasional trophic ulcers on the foot. Then the limb became indurated and hot and the subcutaneous veins became pulsatile, tortuous and enormously dilated. This time it was considered advisable to disarticulate the knee. Healing of the stump subsequently occurred.

ABRAMSON

CORONARY ARTERY DISEASE

Bloch, E. H.: "In vivo" Microscopic Observations of the Circulating Blood in Acute Myocardial Infarction. Am. J. M. Sc. **229:** 280 (March), 1955.

The stereobinocular microscope was employed to examine the details of blood flow through the conjunctival vessels of 205 control patients and 75 patients with acute myocardial infarction. The fluidity and flow characteristics of the blood were evaluated before and after the use of anticoagulant drugs, heparin, Dicumarol and Tromexan in the latter groups, in order to use each subject as his own control and for comparison with the noninfarction group. The microscopic reactions observed in the controls were those of a rapid flow through arterioles and venules with individual erythrocytes identifiable in capillaries; hypertensive patients showed some degree of microscopic anemia in arterioles. In the presence of minor infections, serial observations reveal a transitory aggregation of erythrocytes in smaller venules which disappeared as symptoms abated. In myocardial infarction, after 24 or 48 hours the majority of erythrocytes were stuck into aggregates, a few of which intermittently plugged arterioles for 1 to 20 seconds. In the venules, the blood became dark red with dense masses of erythrocytes. The walls of venules became more permeable to plasma fluids creating local edema, sacculations and minute hemorrhages. There was a decrease in the velocity of flow with increased tortuosity and hypertrophy of the venules. Within a fortnight, most of the intravascular and vascular changes receded. In the more acutely ill patients with "shock," the conjunctiva was relatively avascular with occasional areas of rigid erythrocyte aggregates observed in arterioles. The use of anticoagulants did not significantly influence the microscopic pattern. The physical characteristics of the erythrocyte aggregates were not altered when the prothrombin time fluctuated between 10 and 40 per cent of normal. The abnormality of the venular wall was increased by the anticoagulant above that produced by the flow abnormalities. The evidence shows that anticoagulants do not revert the blood to its normal fluidity. The intravascular changes disappeared or waned as clinical improvement occurred.

SHUMAN

Schnebli, M.: The Clinic of Myocardial Infarction. Cardiologia **26:** 129 (Fasc. 3), 1955.

The author reviews the case histories of 300 patients treated from 1949 to 1954 for recent myocardial infarction at the University Hospital in Zürich. Of these, 214 were males and 86 females; the mortality during their hospital stay was 45 per cent. Underlying or associated pathologic conditions were hypertension, obesity and diabetes in 53 per cent, and an infection in 29 per cent. A prodromal stage occurred in 31 per cent in the form of anginal pain, in 22 per cent as development of heart failure and in 27 per cent as a combination of both. In 70 per cent, the presenting symptom at the time of infarction was precordial pain, in 49 per cent radiating peripherally. In 30 per cent there was no pain at any time. The electrocardiogram showed typical changes in 62 per cent and was atypical in 38 per cent, due to multiple infarction, or the association with an intraventricular conduction defect.

None of the patients treated by anticoagulants developed venous thrombosis or peripheral emboli. The death rate, due to pulmonary, cerebral, or renal emboli, was 32.8 per cent in the untreated group, in contrast to no death in the group receiving anticoagulant treatment. The following factors permit, according to the author, a favorable prognosis: age under 50, a short prodromal stage, slight rise in the sedimentation rate, infarction of the posterior wall, and early medical treatment.

PICK

Ravdin, I. S., Fitz-Hugh, T., Jr., Wolferth, C. C., Barbieri; E. A. and Ravdin, R. G.: Relation of Gallstone Disease to Angina Pectoris. Arch. Surg. **70:** 333 (March), 1955.

The authors present a number of case histories in an attempt to cast light on the relationship of gallstone disease to angina pectoris. They pointed out that gallstone disease is capable of producing localized spasm in the gastrointestinal tract and that when the response is present in the esophagus, especially the lower part, the pain may simulate angina pectoris. Furthermore, the pains regarded as anginal in patients with gallstone disease are often unrelated to effort and most frequently occur at night while the patient is at rest in bed.

There seems to be little doubt that anginal pain can be excited in susceptible patients by gall bladder disturbance. The complete relief that at times follows operation can be explained on the basis of removal of extrinsic factors originating in the diseased gall bladder and causing narrowing of coronary vessels, lessening of coronary flow and precipitation of anginal seizures. However, operation upon the biliary tract should not be undertaken solely for the purpose of relieving anginal pain, unless the evidence is clear cut for a relationship between the symptom and biliary tract disease.

On the other hand, the diagnosis of the anginal syndrome should not be regarded as a contraindication to an operation upon a diseased biliary tract, except when the heart disease is so far advanced that the operative hazard outweighs the chance of benefit.

ABRAMSON

Jackson, R. S., Wilkinson, C. F., Jr., Meyers, L. Bruno, M. S. and Benjamin, M. R.: An Evaluation of the Effect of Choline and Inositol on the Clinical Course and Serum Lipids in Patient

with Angina Pectoris. Ann. Int. Med. **42:** 583 (March), 1955.

Forty patients with angina pectoris were studied in a doubleblind experiment to test the effect of a choline-inositol syrup, containing 3.0 Gm. of choline and 0.45 Gm. of inositol per 15 cc., on their symptoms and on the levels of their plasma lipids. No statistically significant symptomatic improvement could be demonstrated. The mean levels of plasma cholesterol and phospholipid were significantly higher during choline-inositol therapy. Fluctuations of plasma, cholesterol, and phospholipid were not significantly affected by the choline-inositol treatment.

WENDKOS

Martelle, R. T.: Coronary Thrombosis in a Five-Month Old Infant. Pediat. **46:** 322 (March), 1955.

A 5 month-old infant was brought to the hospital, having been ill for one month previously with "flu." He had been fretful, ate poorly and preferred to be held upright rather than to be left lying down. He was thought to be cyanotic shortly before being brought to the hospital. During the initial examination he died suddenly and without any apparent respiratory distress. At autopsy his heart grossly was thought to show a myocardial infarction due to thrombosis of the left coronary artery. On microscopic section, however, there was evidence of a widespread myocarditis of fairly long duration with necrosis of the myocardium and great infiltration with inflammatory cells. The thrombosis was a terminal situation in this picture. The authors think that this is an instance of rheumatic myocarditis with arteritis and thrombosis secondary to this.

HARVEY

Spain, D. M., Bradess, V. A. and Greenblatt, T. J.: Postmortem Studies on Coronary Atherosclerosis, Serum Beta Lipoproteins and Somatotypes. Am. J. M. Sc. **229:** 294 (March), 1955.

The relationship between serum β-lipoprotein, somatotype and degree of atherosclerosis of the coronary arteries was studied in 157 persons who had died suddenly by violence or from coronary occlusion. Blood for the lipoprotein determination was withdrawn from the heart at autopsy, usually within six hours of death. No change in the lipoprotein concentration was noted over a range of 3 to 20 hours in five instances in which comparative studies were performed to establish the validity of this procedure. A positive correlation between abnormalities in the serum lipoprotein pattern and the degree of vascular sclerosis was found in 84 per cent of the cases. There was lack of correlation in 16 per cent with some of the patients having a normal lipid pattern and advanced sclerosis, while others had abnormal lipids and no vascular sclerosis. In the somatotype subdivisions, the ectomorphic group of males showed the least degree of positive correlation; in the other groups there was a 90 per cent correlation. The evidence indicates that, with the exception of the ectomorphic male, any person having an abnormal serum β-lipoprotein pattern must be regarded as a potential victim of atherosclerosis. This applies most particularly to the mesomorphic male.

SHUMAN

Liebow, I. M., Hellerstein, H. K. and Miller, M.: Arteriosclerotic Heart Disease in Diabetes Mellitus. A Clinical Study of 383 Patients. Am. J. Med. **18:** 438 (March), 1955.

A cardiac survey of 383 living, outpatient diabetic patients discloses 42 per cent had arteriosclerotic heart disease; an additional 16.2 per cent had arteriosclerosis of the aorta; 10.2 per cent had angina pectoris; 6.8 per cent had myocardial infarction. The prevalence of arteriosclerotic heart disease was related in positive manner to sex, age and the presence of hypertension, but was unrelated to the total serum cholesterol level, the degree of control of the diabetes, the patient's weight, the daily insulin dose or the duration of the diabetes.

HARRIS

Case, R. B., Berglund, E. and Sarnoff, S. J.: Ventricular Function. VII. Changes in Coronary Resistance and Ventricular Function Resulting from Acutely Induced Anemia and the Effect thereon of Coronary Stenosis. Am. J. Med. **18:** 397 (March), 1955.

The response of the circulatory system to anemia is manifested by significant changes among which are tachycardia, increased cardiac output, a fall in peripheral resistance and cardiomegaly. The authors investigated the extent to which coronary vessels participate in the response to anemia and compensate for the reduced oxygen carrying capacity of the blood in the open-chest, narcotized dog with a complete circulation. They found a greater coronary flow per unit of left ventricular work occurs during anemia. The increment was a function of the severity of the anemia. The decreased oxygen carrying capacity of the blood was largely compensated for by an increased coronary flow which resulted from lower coronary resistance. The resistance decreased progressively as the hematocrit was reduced and approached a minimal value at low hematocrit levels. More complete removal of oxygen from coronary blood was a limited but significant factor. Depression of the ventricular function curve (less work per unit of filling pressure) did not occur until the hematocrit was reduced to between 24 and 31 per cent. After this, the curve was progressively depressed as the hematocrit was decreased. The apparent cause of the depression of the ventricular function curve in severe anemia is that the coronary vessels have approached maximal dilatation and cannot further compensate for the decreased oxygen carrying capacity of the blood. In the presence of coronary

stenosis, anemia accentuated the depression of ventricular function. The presence of a substantial vasodilatory reserve at high work loads with a normal hematocrit suggests that, under these circumstances, maximal ventricular stroke work is not limited by the availability of oxygen, but is determined by factors within the heart muscle itself.

HARRIS

Boyer, N. H.: Digitalis in Acute Myocardial Infarction. New England J. Med. **252:** 536 (March 31), 1955.

The author presents a general report concerning his experience with the use of digitalis in acute myocardial infarction. He has used digitalis freely and has yet to encounter any ill effects directly attributable to the drug. It is reported that in a series of 50 consecutive patients, with proved fresh myocardial infarction and who received digitalis, the mortality was 16 per cent. It is pointed out that this uncontrolled series does not permit a definite conclusion that digitalis influenced the course of the disease favorably, but it can be concluded that when used carefully in myocardial infarction, it rarely results in the dire consequences which have been predicted freely in medical writings. It has not been necessary to use quinidine or Pronestyl along with the digitalis. It is concluded that digitalis is frequently indicated in myocardial infarction and may, indeed, be life saving.

ROSENBAUM

Lesher, N., Sherrod, T. R. and Killam, K. F.: Alcohol on the Coronary Circulation of the Dog. J. Pharmacol. and Exper. Therap. **113:** 414 (April), 1955.

The effect of alcohol on the coronary circulation has never been clearly defined. Coronary sinus outflow and arterial inflow into the circumflex branch of the left coronary artery were measured in open chested anesthetized dogs by means of modified Morowitz cannuli and an electric recording rotometer interposed between the carotid artery and the circumflex branch of the left coronary artery.

Rapid intravenous injection over 20 seconds of 250, 375 and 500 mg. per Kg. body weight of ethanol produced no significant change, a maximal increase of 60 per cent and 117 per cent respectively in coronary sinus outflow. Coronary artery inflow did not change with the ethanol dose of 250 mg. per Kg. but increased 24 to 39 per cent with 375 mg. per Kg. and 36 to 101 per cent with 500 mg. per Kg. At the time of this maximal increase there was a significant decrease in mean arterial blood pressure without any change in heart rate. Slow intravenous injection over 35 minutes of a 10 per cent ethanol solution until a total dose of 500 mg. per Kg. was given produced an average maximal increase of 30 per cent in coronary sinus outflow. There was a significant lowering of blood pressure and heart rate. Ethanol was compared to various doses of aminophylline and papaverine hydrochloride on close arterial injections into the circumflex branch of the left coronary artery. Ethanol was found to be less effective than these other drugs.

Ethanol (ethyl alcohol) increased both coronary outflow and inflow of the anesthetized dog at blood levels similar to those obtained following the oral ingestion of moderate amounts of alcohol (2 or 3 cocktails) in man. Ethanol was less effective than papaverine hydrochloride and aminophylline. However, intestinal absorption of ethanol is better than that of the other two agents.

WECHSLER

CONGESTIVE HEART FAILURE

Oketa, G. T., Talso, P. J., Curry, J. H., Smith, F. D. and Geiling, E. M. K.: Blood Level Studies of C^{14}-Digitoxin in Human Subjects with Cardiac Failure. J. Pharmacol. & Exper. Therap. **113:** 376 (April), 1955.

The rate of disappearance of digitalis from the blood stream of humans is not known. With the introduction of labeling of Digitoxin with C^{14}, it is now possible to measure the rate of disappearance of unchanged Digitoxin and its conversion products from the blood stream of cardiac patients.

One-half mg. of radioactive Digitoxin was injected intravenously into four patients with varying degrees of congestive failure. In four others with congestive failure, 1.2 mg. was injected intravenously. Blood samples were drawn over a 96-hour period following the injections and the radioactivity of unchanged Digitoxin (separated chemically) and its conversion products were measured by means of an internal gas-flow Geiger counter.

Blood levels indicate that approximately 42 per cent of the injected dose can be detected in the blood as unchanged Digitoxin 2 minutes after the injection, 12 per cent after 15 minutes, 6 per cent after 1 hour, 3 per cent after 6 hours, 2 per cent after 24 hours and 1 per cent after 96 hours. Two rate constants were found for the disappearance rate of unchanged Digitoxin from the blood. The biologic halflife of the first component is 15 to 30 minutes, of the second 48 to 54 hours. There was no difference in these values with the two doses studied. The first component or rapid rate is assumed to represent the rate at which Digitoxin is equilibrated with body tissues and the second component or slow rate may represent the rate at which Digitoxin is being liberated from the body tissues.

Blood levels and disappearance rates from the blood of radioactive Digitoxin have been measured in eight patients with varying degrees of congestive failure.

WECHSLER

Jóstér, T. and Pinter, J.: Serum Protein Fractions in Heart Failure. Cardiologia **26:** 182(Fasc. 3), 1955.

The authors used paper electrophoresis to study the serum protein fractions in cardiac patients. They made 79 determinations in 50 patients with heart failure and one determination in each of 30 controls. Patients with heart failure showed a reduction of the α_2, β and γ globulins. In patients refractory to digitalis therapy, a marked decrease in the albumin content was noted. Quantitatively, there appeared to be a correlation between the degree of abnormality of serum protein fractions and the severity of the cardiac condition. Although these biochemical alterations are primarily attributable to hepatic congestion, an abnormal composition of the serum protein was also found in cases with left ventricular failure in the absence of a congested liver. The latter finding is most likely due to the poor nutritional stage of patients with congestive heart failure. The authors conclude that intake of large amounts of protein, particularly albumin, should be encouraged in cases with advanced congestive failure.

PICK

Braun, K., and Izak, G.: Acute Pulmonary Infection and Cardiac Failure in Chronic Emphysema. Am. Heart J. **49:** 385 (March), 1955.

Clinical and laboratory observations were made in seven patients (ages 29 to 65 years; 2 females, 5 males) suffering from pulmonary emphysema and chronic bronchitis in whom acute pulmonary infection was found to be responsible for the development of congestive heart failure. Serial pulmonary function tests were performed during the period of observation. Treatment consisted of a low sodium diet, intermittent oxygen breathing and injections of penicillin, streptomycin or administration of aureomycin, as indicated by the in vitro sensitivity of the microorganisms cultured from the sputum. Xanthine preparations were given parenterally or per os and epinephrine by inhalation. In three cases, digitalis and mercurial diuretics were used. The period of observation and treatment lasted between 12 and 14 days. There was a close correlation between the degree of pulmonary insufficiency and the severity of congestive heart failure. Recovery from the acute pulmonary infection was followed by the disappearance of the signs of cardiac failure. In two cases, breathing of concentrated oxygen increased respiratory acidosis.

RINZLER

Hudson, W. E., Hollander, W., Hatcher, J. D., Halperin, M. H. and Friedman, I. H.: The Cardiohemodynamic Effects of Venous Congestion of the Legs or of Phlebotomy in Patients with and without Congestive Heart Failure. J. Clin. Invest. **34:** 614 (April), 1955.

The fall in cardiac output following venous congestion of the legs has been attributed to a decrease in right atrial pressure. In this study of cardiohemodynamics in man, as measured by intracardiac catheterization, patients with cor pulmonale (with or without failure) had a fall in cardiac output during venesection or venous occlusion. However, patients with congestive failure due to hypertensive, coronary or valvular disease usually had a slight rise, occasionally no change or, rarely, a slight fall in output. These and other observations suggest that in hypertensive heart disease, without failure, and in cor pulmonale, with or without failure, the heart may be more responsive to changes in right heart filling, while in patients with só-called low output failure, the heart is less responsive to such changes.

WAIFE

Kessleman, R. H.: The Formation of Edema and the Effect of Sodium on Colloid Osmotic Pressure. Am. Heart J. **49:** 517 (April), 1955.

This paper deals with the physicochemical relations between electrolyte concentration and colloid osmotic pressure. Calculations made with known data demonstrate that depression of plasma sodium raises plasma colloid osmotic pressure and vice versa. This is an important controlling mechanism in the distribution of fluid in the intravascular and interstitial fluid components.

RINZLER

ENDOCRINE EFFECTS ON CIRCULATION

Starr, P. and Liebhold-Schueck, R.: The Effect of Levo-Thyroxine, Dextro-Thyroxine and Levo-tri-Iodo-Thyronine on the Electrocardiogram in Myxedema: Preliminary Report. Ann. Int. Med. **42:** 595 (March), 1955.

Five cases of myxedema were treated with three thyroxine isomers. In several cases, the electrocardiogram began to change toward normal and occasionally became normal before the serum protein-bound iodine or metabolic rate became normal. This was by no means constant, but was so frequent as to suggest that the pharmacodynamic action, i.e., the potentiation of the epinephrine effect on the heart, was occurring before the general elevation of body metabolism was produced by the medication. The usual understanding is that the heart responds to the metabolic demands of the body for more oxygen. These serial measurements suggest that the heart is affected by the thyroid hormone directly, possibly via the adrenergic substances, the histochemical or the cellular changes, and is not merely responding to an increased work load. These observations reemphasize the classic dictum that the treatment of myxedema begins with a fraction of the final maintenance dose because of danger to the heart. They seem to indicate that the danger lies in the pharma-

codynamic actiod of the thyroxine on the pathologic heart muscle and not in its ability to raise the metabolic rate.

WENDKOS

Harrison, J. H., Leman, C., Munson, P. L. and Laidlow, J. C.: Hormone Excretion Before and After Castration and Adrenalectomy. New England J. Med. **252:** 425 (March), 1955.

This report is based upon animal assay studies and colorimetric measurement of 17-ketosteroids in a small group of patients before and after castration for carcinoma of the prostate and in some patients before and after total adrenalectomy. Biologic assay of urinary androgens in four men disclosed a definite decrease in androgen excretion after castration. Administration of corticotropin (ACTH) to these same patients resulted in an elevation in the androgen excretion of at least 100 per cent in both the intact and castrated men. Castration was followed by a prompt rise in the excretion of follicle-stimulating hormone (FSH). Estrogen therapy did not appear to affect the FSH level in three castrated men studied after administration of TACE. Castration produced no consistent change in the urinary 17-ketosteroid excretion. Total adrenalectomy in the castrated men caused a further reduction of the biologic androgen excretion, but even temporary withdrawal of cortisone for as long as five days did not eliminate androgen activity in the urine completely.

ROSENBAUM

Walser, M., Seldin, D. W., and Burnett, C. H.: Blood Volume and Extracellular Fluid Volume During Administration of ACTH and Cortisone. Am. J. Med. **18:** 454 (March), 1955.

The effects of cortisone and ACTH on blood volume and extracellular fluid volumes have been studied in normotensive subjects without renal or cardiac disease under conditions of salt restriction and controlled salt intake. When salt was restricted, blood volume did not change significantly but the volume of fluid available for dilution of radiosulfate increased slightly, the increment being derived from internal sources. When salt was supplied, extracellular fluid expanded considerably but venous pressure and plasma protein concentration did not change significantly. Blood and plasma volume remained constant or fell slightly as extracellular fluid volume expanded, and failed to reflect day-to-day fluctuations in the interstitial space. The stimulus which promotes renal adjustment to an excess of interstitial fluid apparently need not involve blood volume, venous pressure, or plasma oncotic pressure.

HARRIS

Mendelsohn, M. L. and Pearson, O. H.: Alterations in Water and Salt Metabolism after Bilateral Adrenalectomy in Man. J. Clin. Endocrinol. **15:** 409 (April), 1955.

Six patients with metastatic carcinoma, who were well maintained by cortisone after bilateral adrenalectomy, were studied for the effects of cortisone withdrawal on water and salt metabolism by using metabolic balance methods. In addition in two of the subjects, determinations of volumes of distribution of inulin, antipyrine and radioactive sodium were made. Profound clinical collapse occurred in all patients within 3 to 7 days after withdrawal of cortisone.

Water retention was the most frequently observed metabolic change following cortisone withdrawal. In the two patients studied, there was an apparent expansion of the inulin space of 15 and 21 per cent, respectively, during cortisone withdrawal without significant alterations in antipyrine space or in total exchangeable sodium. Hyponatremia developed in four subjects, unassociated with significant renal salt-wastage. In fact the syndrome of renal salt-wasting, hyponatremia, dehydration, hemoconcentration and hyperkaliemia did not occur in its entirety in any of the seven cortisone withdrawal experiments described. In terms of salt and water metabolism, there was no one consistent pattern that could be associated with the inevitable clinical collapse that followed omission of cortisone in the adrenalectomized patients. The disparity between the results reported in this study and the results in experimental animals or Addisonian patients may be attributable to the fact that cortisone alone was used as replacement therapy following bilateral adrenalectomy, without the additional use of a specific saltretaining component.

CORTELL

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY AND BALLISTOCARDIOGRAPHY

Gelfand, D., Urbach, J. R., Bellet, S. and Allison, W.: Right Ventricular Hypertrophy: A Study of the QRSsÊ Loop of the Spatial Vectorcardiogram Employing Cube and Tetrahedron Co-ordinates. Cardiologia **26:** 228 (Fasc. 4.), 1955.

The authors present a comparative study of the vectorcardiogram in right ventricular hypertrophy recorded with the cube and tetrahedron lead system. The material comprises 42 cases with rheumatic and congenital heart disease and chronic cor pulmonale, with right heart strain in the electrocardiogram, excluding instances with combined heart strain, complete and incomplete right bundle branch system block, myocardial infarction and heart failure.

In cases with *advanced* right ventricular hypertrophy, with a diagnostic scalar electrocardiogram, the direction of the QRSsÊ loop was invariably reversed in the horizontal and/or sagittal plane. In 12

p tients with rheumatic heart disease, one with cong nital heart disease and three with cor pulmonale, t e QRSsÊ rotated in the horizontal plane in clockw se direction when recorded with the tetrahedron s stem and anti-clockwise with the cube technic. In t is group, the electrocardiogram was not diagnostic i two cases with cor pulmonale and in three of the r eumatics. Restitution to a normal rotation of the h rizontal loop was noted in one case, six months a ter mitral surgery. The authors conclude that the t trahedron lead system provides a more sensitive m thod in diagnosing milder degrees of right ventr cular hypertrophy than the cube system and the s alar electrocardiogram. This can be explained by t e concept of differences between anatomic and e ectrically effective axes as emphasized by Schaffer.

PICK

Schaub, F., Vögtlin, J. and Bühlmann, A.: The Relation between Electrocardiographic Alterations in Right Ventricular Hypertrophy and Hemodynamics of the Pulmonary Circulation in Congenital Malformations in Mitral Stenosis and Chronic Cor Pulmonale. Cardiologia **26:** 209 (Fasc. 4), 1955.

In 19 cases with congenital heart disease, in 31 with mitral stenosis, and in 35 with chronic cor pulmonale, the various manifestations of right ventricular hypertrophy in the precordial electrocardiogram were compared with the mean pulmonary arterial pressure, the total resistance to pulmonary flow and the calculated work of the right ventricle. The best correlations with hemodynamic data were found in the size of the R wave in V_1. It could be shown that, to a certain extent, the amplitude of this deflection increased in direct proportion to the pulmonary artery pressure in congenital and mitral lesions, to pulmonary vascular resistance in mitral disease and to the work of the right ventricle in cor pulmonale. From hemodynamic alterations found in cases with an R in $V_1 > 5$ mm., it may be concluded that this, per se, is a reliable electrocardiographic sign of right ventricular hypertrophy, even in the absence of an abnormal R/S ratio, provided this is in agreement with clinical findings. The incidence of abnormal electrocardiograms, in anatomically confirmed right ventricular hypertrophy and the relation of electrocardiographic and functional alterations in the lesser circulation, are discussed.

PICK

Weyn, J. B., Leatham, A., Lian, C., Maass, H. and Minot, G.: Standardization of Phonocardiography. Cardiologia **26:** 252 (Fasc. 4), 1955.

At two joint meetings of cardiologists from various European countries, held in Paris in 1950 and 1953, the following agreements were reached on standardization of phonocardiographic records: vibrations below 15 and above 800 Hertz should not be recorded; in addition to standard records, recordings comprising the middle perception range of the human ear should be made with the help of special filters; the film speed should be 5 to 10 cm. per second; a statement should be made with each record concerning filters used and the position of the microphone on the chest wall.

PICK

Wenger, R., Massumi, R. A. and Kuramoto, K.: A Comparative Study of Esophageal and Direct Auricular Electrocardiography in Dogs. Cardiologia **26:** 193 (Fasc. 4), 1955.

In order to clarify the genesis of the atrial deflections in the canine esophageal electrocardiogram, records were obtained on 15 dogs, on 7 with wide open chest, esophageal direct atrial electrodes being placed at various, exactly corresponding transverse levels. By simultaneous recordings of the two curves it was possible to compare the arrival time of the activation wave at various areas of the atria, and their transmission to the atria.

Since the dog's esophagus, when compared with the anatomical situation in man, is located more to the right and hence in closer relation to the right than left atrium, the shape of the esophageal curve differs in the two species. The patterns of the most cranially and caudally registered esophageal electrocardiograms showed intrinsic deflections caused by right atrial potentials only. However, alterations of the esophageal leads could be produced by injury to the left atrium and this indicates that the contour of the esophageal electrocardiogram is to some extent influenced by potentials of both atria, the degree of each component varying with the position of the esophageal electrode relative to the two chambers. A study of the spread of the activation wave through the atria seemed to indicate that activation of the posterior left atrial wall takes place relatively early and is accomplished in a right to left direction. The lateral aspect of the right atrium is activated earlier than corresponding points at its anterior wall which suggests a more rapid transmission of the sinus impulse along the lateral wall.

PICK

Wasserburger, R. H.: Observations on the "Juvenile Pattern" of Adult Negro Males. Am. J. Med. **18:** 428 (March), 1955.

The author discusses the common occurrence of an unusual electrocardiographic pattern in the adult Negro male which consists of frank inversion of the T waves in the right and mid-precordial leads with lesser change reflected in the standard and augmented limb leads. Because of the close similarity in the T wave configuration of this particular pattern to that seen in infants and young children, it has been referred to as the "juvenile pattern." Of 131 adult Negro males, 14 (10.8 per cent) showed

this pattern despite normal cardiovascular systems with no evidence of pericarditis. The administration of 10 Gm. of potassium bicarbonate-citrate mixture orally or 20 to 30 mg. of Pro-Banthine intravenously consistently normalized the juvenile pattern. Hyperventilation constantly exaggerated the T wave inversion pattern, an effect which could be abolished by the administration of Pro-Banthine. The "juvenile pattern" represents an expression of hypervagotonia and is considered to be a normal variant in the adult Negro. Caution must be used in the interpretation of these transient electrocardiograms in the adult Negro if erroneous diagnoses of "subepicardial myocarditis," "myocardial ischemia" and "subacute pericarditis" are to be avoided and the risk of promoting serious iatrogenic heart disease eliminated.

HARRIS

Bateman, R. D. and January, L. E.: The Precordial Electrocardiogram in Mitral Regurgitation. Am. J. Med. **18:** 415 (March), 1955.

Reviewing the precordial electrocardiograms of 61 patients with disease of the mitral valve, the authors found that the group of patients with significant mitral regurgitation had a distinctly later onset of the intrinsicoid deflection and greater voltages of S waves in V_1 and R waves in V_5 or V_6 than did the patients with relatively "pure" mitral stenosis. They suggest that the precordial electrocardiogram, when carefully correlated with the history, physical examination and roentgenologic findings, should be of definite value in detecting minor degrees of left ventricular hypertrophy in patients with dynamically significant mitral regurgitation in whom physical examination, cardiac fluoroscopy and pulmonary artery "wedge" pressures, alone or in combination, may fail.

HARRIS

Smith, J. E., Lederer, L. G. and Mandes, J. C.: Evaluation of the Calibrated Displacement, Velocity, and Acceleration Ballistocardiograph in Angina Pectoris. Am. Heart J. **49:** 344 (March), 1955.

Calibrated displacement, velocity and acceleration ballistocardiographs were taken on 15 patients with typical and 5 patients with atypical angina pectoris. Fourteen of these patients had normal resting electrocardiograms and six borderline resting electrocardiograms. Ten of the group had positive exercise tests. Eight illustrative examples of patients between the ages of 33 and 53 are given. The authors compared the amplitudes of the displacement IJ segments in 50 normal subjects between 20 and 40 years of age and the 20 cases of angina pectoris. The normal patients always had displacements of 0.0014 inches or more and the angina patients 0.0016 inches or less so that the overlap was small. The acceleration curve revealed abnormalities in shape and wave form more consistently than the others. The authors believe that with proper attention to instrumentation, the ballistocardiograph may be a more sensitive indicato of coronary artery disease than is the electrocardio graph.

RINZLER

Scher, A. M.: Direct Recording from the A-V Conducting System in the Dog and Monkey. Scienc **121:** 398 (March 18), 1955.

Exploring electrodes were inserted into the inter atrial septum anterior to the coronary sinus in th area of the A-V node as noted by Tawara. Othe electrodes were placed in the interatrial interven tricular septa along the conducting bundle and it branches, as well as in the apical ventricular cavit where preterminal branches constitute "false ten dons."

Potentials varied considerably and, at present, n statement can be made regarding the nature of th A-V nodal delay or nodal activation.

The conduction rate in the more central part o the system is nearer the 2 meters per second rate calculated for transmission in false tendon, than th 1 meter per second in the lining of the ventricular wall. No appreciable delay between activation of the terminal portions of the conducting system and ventricular musculature activation, was found.

WAIFE

Sayers, B. McA.: A Spatial Magnitude Electrocardiograph. Am. Heart J. **49:** 336 (March), 1955.

Details are presented of a spatial magnitude electrocardiograph which plots the total effective magnitude of the equivalent cardiac dipole as a function of time. The processes of squaring, adding, square root taking and integration are described and the accuracy of the procedures briefly discussed.

RINZLER

Fagin, I. D. and McIntyre, K. E.: Experiences with Ballistocardiography. Ann. Int. Med. **42:** 995 (May), 1955.

Since the per cent incidence of normal, abnormal and borderline ballistocardiographic curves was essentially the same in the healthy subjects, in the subjects with emotional disorders and in the subjects with diseases not involving the cardiovascular systems, these three groups were combined into one group exhibiting no clinical evidence of cardiovascular disease. This group is compared with the subjects who had clinical evidence of cardiovascular disease, with respect to the per cent incidence of normal, abnormal and borderline curves. Both groups are subdivided according to age, since in the population at large the percentage of abnormal curves increases with increasing age. Analysis of the data indicates that there are no striking differences between the groups with and those without clinically recognizable cardiovascular disease in any of the age groups.

The greatest discrepancy is in the 41 to 60 years group, wherein 58 per cent of the noncardiacs had normal ballistocardiograms, while 32 per cent of the cardiacs had normal curves. In the age group of 61 years and older, the percentages are almost identical. Granting the relative smallness of the samples, it seems that the ballistocardiogram is not reliable as a screening method to differentiate cardiacs from noncardiacs. In these studies, there was no specificity of abnormal wave pattern for cardiac lesions. Just as bundle branch block may be found in many etiologic categories of heart disease, so were similar abnormalities of ballistocardiographic wave pattern found in different types of heart disease. In the one case of coarctation of the aorta which was encountered, the ballistocardiogram was perfectly normal and did not exhibit the shortening of the K wave usual in such cases. All severely disabled cardiacs (functional class IV) had abnormal ballistocardiograms. However, in asymptomatic cardiacs or in mild to moderately symptomatic cardiacs the ballistocardiograms ranged from normal through abnormal without any exact correlation between the degree of clinical disability and the abnormality of the ballistocardiogram. In general, healthy young subjects tended to have normal ballistocardiograms, but so did young cardiacs. A diagnosis of cardiac impairment should not be made solely on the basis of an abnormal ballistocardiogram. Cardiac neuroses are too readily produced in susceptible individuals and misuse of the ballistocardiogram may lead to an increase in so-called iatrogenic heart disease. Ballistocardiography is a very interesting experimental approach to cardiovascular dynamics. Its future depends on improvement in recording systems, understanding or elimination of extravascular corporeal distortions, perfection of summating or integrating technics to permit measurement of the cardiovascular forces in more than just one direction and better correlation of the ballistocardiogram with other physiologic events in the cardiac cycle.

WENDKOS

HYPERTENSION

Joly, F., Mathivat, A., Sicot, J. R., Gerbaux, L. and Touche, M.: Extensive Sympathectomy in Arterial Hypertension. Arch. mal. coeur **48:** 245 (March), 1955.

The authors report a follow-up study on 80 cases of hypertension (out of a series of 122) submitted to bilateral dorsolumbar sympathectomy. With proper selection of the patients, the operative mortality in this series became less than 2 per cent. Of the 80 patients, 23 died within 1 to 5 months following surgery and of the 57 survivors, observed over two to six years, 19 showed complete, 17 partial and 22 one or only transitory regression of the hypertension syndrome.

The actual blood pressure value does not reflect completely the effects of the operation. Permanent reduction of the blood pressure does not eliminate the dangers of serious renal and cerebral complications and, contrariwise, persistence of an elevated pressure does not rule against success of the operation. The beneficial effects of sympathectomy consist in regression of retinal hemorrhage and papilledema, reduction of heart size and electrocardiographic signs of left heart strain. Prevention of cardiovascular accidents by the operation remains doubtful. Generally, the sympathectomy rests largely on individual conditions. Most candidates for surgery will be found among younger hypertensives with pronounced symptoms, with a single recent neurologic accident and without severe impairment of cardiac or renal function.

PICK

Dahl, L. K., Stall, B. G., III, and Cotzias, G. C.: Metabolic Effects of Marked Sodium Restriction in Hypertensive Patients. Skin Electrolyte Losses. J. Clin. Invest. **34:** 462 (March), 1955.

Seven subjects, one normal and six with hypertension, were on a low sodium chloride, normal potassium diet for periods of from 26 to 150 days. By a special technic, the skin loss of various electrolytes was determined. These losses were small but despite rigid dietary restrictions, electrolytic balance was possible among the six with good renal function.

Because the absolute skin losses were similar, it was proposed that at some unknown concentration on the skin surface, electrolyte reabsorption begins and continues by a process which is the reverse of that during insensible perspiration.

WAIFE

Ledbetter, P. V. and Morrow, E. J.: Thirty-Three Years' Experience in the Management of Arterial Hypertension. J. Am. Geriatrics Soc. **3:** 172 (March), 1955.

The authors summarize their present ideas of therapy for hypertension on the basis of records gathered from 50,000 patients seen by an internist's during 33 years. Many individuals with slight diastolic hypertension and systolic hypertension need no treatment other than reassurance. Lumbodorsal sympathectomy is seldom necessary, bilateral adrenalectomy, never. Following surgical procedures for unilateral kidney disease in two patients and for pheochromocytoma in one, previously high blood pressures returned to normal. Many abnormally high blood pressures may be lowered to a desirable level with a combination of *Rauwolfia serpentina* and a *Veratrum viride* product; sometimes *Rauwolfia* alone is effective and on occasion hydrazineophthalizine must be added. Patients with headache are often relieved by controlled thiocyanate therapy. A few patients fare well on a low sodium diet; all with heart failure should be placed on this regime. Only medical therapy is indicated in the presence of a persistent, severe renal failure. A blood pressure of

160/100 is a satisfactory level, being sufficiently low to obviate untimely rupture of a vessel in the brain, yet not low enough to interfere with coronary and renal function. The success of treatment also depends upon the physician's encouragement and assistance in the adjustment of these patients to their environment.

RINZLER

Muller, J. C., Rast, C. L., Jr., Pryor, W. W. and Orgain, E. S.: Late Systemic Complications of Hydralazine (Apresoline) Therapy. J.A.M.A. **157:** 894 (March 12), 1955.

During the administration of hydralazine (Apresoline) for the treatment of hypertension, a significant number of important reactions to the drug have been described. These include significant fever, pancytopenia, acute psychoses, gastro-intestinal bleeding and a collagen-like illness. Collagen-like illness was observed in 7 (13 per cent) of 53 patients who received hydralazine for periods of 4 to 23 months. In six patients this illness resembled rheumatoid arthritis and subsided when the dosage of hydralazine was discontinued. In one patient a severe illness manifested by fever, arthritis, pericarditis, pleurisy with effusion and the presence of lupus erythematosus cells developed. This illness closely simulated acute systemic lupus erythematosus and subsides only after hormonal therapy with corticotropin and cortisone. Cell studies obtained in five of the patients with reactions revealed lupus erythematosus cells in two patients. These cells were also observed in two additional patients who remained asymptomatic while receiving hydralazine. In view of the incidence and type of reactions, administration of this drug probably should be reserved for patients with severe hypertensive states.

KITCHELL

Agrest, A., and Hoobler, S. W.: Long-Term Management of Hypertension With Pentolinium Tartrate (Ansolysen). J.A.M.A. **157:** 999 (March 19), 1955.

Thirty-one patients, each of whom had one or more of the serious complications of hypertensive disease or with diastolic blood pressures consistently above 120 mm. Hg on repeated determinations were selected for this study. Ten of these 31 patients had previously had sympathectomy. Dosage was regulated in most cases by the blood pressure response observed at the clinic during all day visits rather than by data obtained from the patient after instructing him in taking his own blood pressure. Treatment was accomplished with orally administered pentolinium tartrate (Ansolysen), with or without reserpine (Serpasil), and hydralazine (Apresoline). This was found to be a simple and safe regimen for the ambulatory management of the hypertensive patients. A median reduction of 38 mm. Hg in the mean daytime standing blood pressure and of 23 mm. Hg in the mean recumbent blood pressure was estimated to have occurred. Improvement in the manifestations of congestive heart failure and of hypertensive retinopathy was observed. The effect of treatment on cerebrovascular complications was less certain but seemed beneficial. Marked relief of moderate uremia or of angina pectoris was seen.

KITCHELL

Sancetta, S. M.: Acute Hemodynamic Effects of Hexamethonium (C6) in Patients with Emphysematous Pulmonary Hypertension. Am. Heart J. **49:** 501 (April), 1955.

The acute effects of intravenously administered hexamethonium were studied in eight subjects with uncomplicated pulmonary emphysematous hypertension. Catheterization criteria included the coexistence of pulmonary diastolic pressures above 10 mm. Hg, pulmonary total resistance of more than 260 centimeter-gram-second and wedge pressure of less than 10 mm. Hg. Data gathered from 10 normal subjects in another study served as control material.

Hexamethonium is effective in producing some reduction in pulmonary artery pressure in the emphysematous subject. Any advantage, however, is counteracted by a profound reduction in brachial artery pressure and venous return. The data indicate that some neurogenic vasomotor control of pulmonary vessels exists in the basal resting state, and that hexamethonium is effective in interrupting this in both the normal and the emphysematous subject. The data do not indicate that an exaggerated degree of vasomotor tone capable of "blockade" at the autonomic ganglionic level exists in the emphysematous subject at rest.

RINZLER

Finnerty, F. A. and Sites, J. G.: The Value of Parenteral Reserpine in Acute Hypertension. Am. J. M. Sc. **229:** 379 (April), 1955.

Reserpine was given intramuscularly or intravenously to 192 patients with acute hypertension due either to toxemia of pregnancy or essential hypertension. An average reduction of 23 mm. Hg in systolic pressure and 19 mm. Hg diastolic pressure was observed in 91 patients, an effect which persisted for an average of six and one-half hours. The most striking effect of the drug was the calming influence with frequent complete relief of anxiety. Veratrum or Apresoline was required to reduce the arterial pressure and control the toxemic state in 71 patients. Reserpine was shown to enhance or prolong the actions of more potent hypotensive agents. As background therapy, reserpine permitted a reduction in dosage of the other drugs, thus lowering their toxicity and facilitating their administration. The toxicity associated with parenteral reserpine therapy included drowsiness, nasal stuffiness, diarrhea and nausea. The depressive action of barbital was mark-

lly enhanced by reserpine. A plan of therapy sug-sted for acute hypertension includes 2.5 mg. of serpine intramuscularly to be repeated every 12 ours and if no hypotensive effect occurs, give 0.5 g. purified veratrum intramuscularly. In seriously patients, reserpine and veratrum can be adminis-red in the same syringe. If this is ineffective, intra-enous veratrum or Apresoline therapy is indicated.

SHUMAN

emmell, A. A.: Phaeochromocytoma and the Obstetrician. J. Obst. & Gynaec. Brit. Emp. **62:** 195 (April), 1955.

Case histories of three pregnant women with phaeochromocytoma are presented and the literature on the subject is reviewed. The author feels that the symptoms are difficult to distinguish from those of eclampsia. He points out that the phaeochromocytoma is a curable condition and thus it should always be considered in the differential diagnosis of eclampsia. In his experience with the three pregnant women with this tumor, operation was successful in one.

HARVEY

Danes, J. N. P. and Short, C. R.: Phaeochromocytoma in a Pregnant African Woman. J. Obst. & Gynaec. Brit. Emp. **62:** 203 (April), 1955.

A case of a phaeochromocytoma in a pregnant African native female is presented. The patient was seen in the hospital three days after onset of labor, still undelivered. At this time she was terminal with high blood pressure and fits. She died within four hours and at autopsy was found to have a phaeochromocytoma. The authors speculate upon the effects of adrenalin and noradrenalin on the uterine contractions.

HARVEY

Rodin, E. A., MacCarty, C. S. and Dockerty, M. B.: Subependymal Glioma with Hypertension: Diagnostic Problem. Proc. Staff Meet., Mayo Clin. **30:** 135 (April), 1955.

A case of tumor of the fourth ventricle in a 58 ear old white male is presented. Histologic study ollowing successful removal revealed it to be a sub-pendymal glioma.

The question arises concerning possible etiologic onnection between the hypertension and the brain umor in this case. Hypertension is usually not a ature of tumors of the fourth ventricle. It appears kely in this case that mild hypertension was ag-avated by the presence of the tumor.

A definite differential diagnosis between hyper-nsive encephalopathy and brain tumor apparently annot be established clinically in some cases. Ven-riculographic studies usually yield the final evi-ence and should be resorted to in cases in which the iagnosis is in doubt. The entire problem would have een purely academic only a few years ago. At present, the differentiation is of vital importance for the future of the patient, since the therapeutic approach is so totally different and since radical operation with removal of the patient's lesion can be performed in one of the most delicate areas of the human brain, namely the fourth ventricle.

SIMON

Dahl, L. K. and Love, R. A.: Evidence for Relationship Between Sodium (Chloride) Intake and Human Essential Hypertension. Arch. Int. Med. **94:** 525 (Oct.), 1954.

A group of 547 adults was classified as having low, average or high NaCl intake. The incidence of hypertension among the three groups was studied. No hypertension was found among those 65 persons classified as having a low NaCl intake; there were 17 hypertensives among the 243 persons in the average intake group; 24 of the 239 persons classed as having a high sodium intake had hypertension. As tested by the chi-square criterion, such a distribution would occur by chance in slightly less than 3 per cent of cases. The hypothesis is proposed that some minimum level of sodium intake must be exceeded for the development of essential hypertension but that, while necessary, sodium is not of itself sufficient for development of the disease.

BERNSTEIN

Schneider, J. A.: Further Characterization of Central Effects of Reserpine (Serpasil). Am. J. Physiol. **181:** 64 (April), 1955.

These experiments demonstrate that reserpine blocks the manifestation of sham rage in cats. However, direct electrical stimulation of the diencephalon still produced a rise in blood pressure after reserpine. Carotid occlusion reflexes were decreased. These experiments support the hypothesis that reserpine blocks centrally, afferent impulses which increase sympathetic activity. Diencephalic centers are not directly depressed.

OPPENHEIMER

Franklin, R. B. and Pollock, B. E.: Thoracic Aorto-Caval Aneurysm. A Review and the Addition of Three Cases. Medicine **34:** 97 (Feb.), 1955.

The authors reviewed 125 proven cases, reported in the literature, of rupture of a thoracic aortic aneurysm into the superior vena cava and added three of their own. This site of the rupture was less common than a rupture into the pericardium or pulmonary artery. The etiology was usually syphilis, but many of the reported cases occurred before serologic tests for syphilis were available. Arteriosclerosis and trauma may also play a role. Features of note in the pathology are the frequency of saccular aneurysms, the predilection for the ascending aorta, the common occurrence of multiple aneurysms and the occasional occurrence of multiple perforations.

The clinical picture is striking. Symptoms attributable to aneurysm may or may not be present prior to rupture. Rupture generally occurred abruptly and dramatically and was followed by the rapid appearance of swelling and cyanosis of the face and neck, dyspnea, choking pain, a sense of heat in the upper parts of the body and evidence of venous engorgement. In many cases a loud, continuous murmur developed at the right second intercostal space.

Diagnostic procedures were rarely necessary. Radiographic studies showed evidence of an aortic aneurysm in 48 out of 49 cases. Angiocardiography was performed in six cases and failed to demonstrate the arterio-venous connection in any. Retrograde arteriography in one case was also unsuccessful in visualizing the communication. Cardiac catheterization in two cases revealed increased pressure and increased oxygen saturation in the superior vena cava. The diagnosis can be made almost with certainty from the clinical picture alone.

The futility of medical treatment was very apparent. Though there may be hope for surgical correction, this has not yet been attempted. The average duration of life, following the rupture, was 42.2 days in 111 cases. In 16 cases, death occurred within 24 hours. There has been one survival of 526 days.

ENSELBERG

Goormaghtigh, N., De Vos, L. and Blancquaert, A.: Ostial Stenosis of Coronary Arteries in a Nine-Year Old Girl. Arch. Int. Med. **95:** 341 (Feb.), 1955.

A report is made of a case of ostial stenosis of the coronary arteries in a girl 9 years, 9 months old. The histologic picture was that of tertiary syphilitic aortitis limited to the region of the ostia and the origin of the coronary arteries. The histologic findings were not corroborated either by clinical examination of the parents or by blood tests of their children or the surviving grandparents. The possibility of second generation syphilis or of accidentally acquired syphilis is discussed. From the clinical point of view, a nonsyphilitic etiology is not ruled out.

BERNSTEIN

Muri, J. W.: Arteriovenous Aneurysm of the Lung. Am. J. Surg. **89:** 265 (Jan.), 1955.

The author discusses the pathologic anatomy, physiology, diagnosis and course of arteriovenous aneurysm of the lung. This condition is probably congenital in origin and in the majority of cases the shunt is from a pulmonary artery to a pulmonary vein. One or more branches from the artery enter the aneurysmal sac which is drained by a greatly enlarged and often tortuous vein. The aneurysmal channel is generally composed of dilated sinusoids which may be partly filled with clot. The condition may be found in any part of the lungs but is most frequently noted in the middle and lower lobes.

Because of the right-to-left shunt, oxygen unsaturation is frequently present in the systemic circulation, leading to secondary polycythemia with augmentation of the cell volume. Plasma volume remains normal or nearly so.

The main complaint is shortness of breath while the outstanding findings are cyanosis and clubbing of the fingers and toes. Nervous symptoms, in the form of headache, numbness and weakness in one side of the body and convulsions, are common in cases with marked cyanosis. Hemoptysis is frequent. Telangiectasis in the skin or the visible mucous membrane is found in more than half the cases. Recurrent epistaxes may be noted. A murmur, sometimes continuous but more often systolic and louder in deep inspiration, is heard in about half the cases.

The most important roentgenographic sign is the finding of a shadow in the lung fields which is round or lobulated and is connected with the pulmonary hilum by broad, band-shaped vascular shadows. With the Valsalva test, the size of the mass will diminish.

If untreated, the disease may remain stationary for years, but frequently there is a definite tendency toward progression. Therapy consists of removal of the aneurysm.

ABRAMSON

Storstein, O. and Austarheim, K.: Progressive Muscular Dystrophy of the Heart. Acta med. scandinav. **150:** 431 (Jan. 29), 1955.

The case of a young man who died at the age 20 of congestive heart failure, due to involvement of the heart associated with progressive muscular dystrophy, is reported in detail. Postmortem examination disclosed a heart which weighed 750 Gm. The myocardium disclosed considerable reduction in the muscle cells with replacement by fatty tissue and a loose, rather edematous connective tissue. The myocardial fibers varied greatly in size with degeneration of the sarcoplasm, loss of striation and fragmentation of nuclei. In some areas only nuclei remained, the rest of the muscle cell having been destroyed. The clinical picture in this patient was of interest. Death occurred only a few months after the first evidence of congestive heart failure appeared and the usual measures of treatment had relatively little beneficial effect. The authors warn against exertion or ambitious rehabilitation programs in patients with this disorder who develop evidence of cardiac involvement.

ROSENBAUM

Yanguas, M. G.: Primary Neurosarcoma of the Heart. Am. J. Roentgenol. **73:** 590 (April), 1955.

Well over 40 cases of primary tumors of the heart have been reported. Besides organized thromb or pseudomyxomas, there have been angiosarcomas

abdomyosarcomas, sacro-epitheliomas, leiomyosarcomas, fibromyxosarcomas, endothelial sarcomas, hemangioendothelial sarcomas, lymphoid or round cell sarcomas, myxosarcomas, giant cell sarcomas, endotheliomas and, in this case report, the first primary neurosarcoma.

The patient presented a mass in the left chest, but no symptoms or manifestations of heart failure or significant electrocardiographic abnormalities, in spite of the destruction of portions of both atrial walls and the posterior portion of the interventricular septum which were seen at necropsy.

SCHWEDEL

ROENTGENOLOGY

Corday, E. and Elkin, M.: Visualization of Caudal Surface of Heart by Use of Carbonated Beverage. J.A.M.A. **157:** 712 (Feb. 26), 1955.

Clinical examination, including routine roentgenography of the heart, often fails to reveal the true extent of downward enlargement of the left ventricle. After seven ounces of a commercial carbonated beverage, such as soda water or ginger ale, has been taken slowly and without eructation, roentgenographic and fluoroscopic examination of the heart visualizes this organ much better because of the artificial production of a stomach bubble. In some patients with enlarged hearts as much as one third of the total anterior surface area of the heart may be completely invisible on routine roentgenogram. The stomach bubble will reveal the true size of these hearts and disclose the true contour of the inferior and apical segments. The heightened contrast also facilitates the search for intracardial and pericardial calcification.

KITCHELL

Lind, J., Spencer, R. and Wegelius, C.: The Diagnosis of Cardiac Shunts by Intravenous Angiocardiography. Brit. Heart J. **16:** 407 (Oct.), 1954.

The authors discuss the value and limitation of high speed, simultaneous biplane angiocardiography in the diagnosis of cardiac shunts.

Right-to-left shunts: Electrocardiographic timing is necessary to identify diastole. The earlier the contrast medium reaches the right atrium or right ventricle in diastole, the more complete the opacification will be. Shunts may not be visualized, if the contrast medium reaches the chamber at an inopportune time or if the axial stream is not visualized. (1) Interatrial systolic shunt: Rapid injection of contrast medium may not appreciably alter atrial systolic pressure and, therefore, may not cause false visualization of a right-to-left shunt unless possibly when the heart rate is slow. (2) Interatrial diastolic shunt: Here, rapid injection may increase pressure sufficiently to produce a false shunt or conversely, late in diastole, a shunt may not be visualized because opacified blood empties directly into the ventricle. The right anterior oblique position helps to differentiate interventricular shunts. Abnormal venous return may be difficult to differentiate. (3) Interventricular shunt: Dilution of contrast medium makes this diagnosis difficult; no sharp jet is seen. If the defect is high, contrast medium may flow directly into the aorta, best seen when the limbs of the ascending and descending aorta are superimposed. (4) Patent ductus arteriosus: Simultaneous visualization of the descending aorta and pulmonary artery with lack of visualization of the ascending aorta is pathognomonic.

Left-to-right shunts: In these instances, enlargement of the lesser circulation with diminution of the caliber of the aorta is seen. The principal of dilution of contrast medium is used. (1) Interatrial shunt: There is a discrepancy between heavy opacification of the vena cava and poor filling of the right atrium in atrial systole. Persistent opacification of the right atrium, right ventricle and pulmonary artery is presumptive evidence of left-to-right interatrial shunt. Reflux into the tributary veins produces opacification similar to that in the atrium. (2) Interventricular shunts: A similar difference in opacification of the right ventricle and right atrium are seen. In a high defect, dilution is localized to the infundibulum and pulmonary artery. The left atrium is strikingly dilated and visualization of the right ventricle and pulmonary artery is prolonged. (3) Patent ductus arteriosus: Early loss of concentration of contrast medium in the pulmonary artery is seen and reaches a maximum at the end of diastole. Persistent visualization of the pulmonary artery, when demonstrable, is likewise characteristic.

SOLOFF

Soloff, L. A., Zatuchni, J. and Fisher, H.: Use of Planigraphy in Demonstration of Calcification of Heart Valves and its Significance. Arch. Int. Med. **95:** 219 (Feb.), 1955.

Planigraphic studies of the heart in 31 patients revealed calcification of the mitral valve alone in nine, of the mitral valve and left atrium in three, of the mitral and aortic valves in nine and of the aortic valve alone in five. Multiple valve lesions were disclosed where none or only one was suspected by all other methods. Valve lesions were discovered in those with cardiomegaly or precordial murmurs of uncertain origin. Calcification of the mitral valve usually produces mitral stenosis and regurgitation. Such calcification increases the risk of the production of more regurgitation and of embolism by mitral commissurotomy.

BERNSTEIN

Eldridge, F. L., Hultgren, H. N., Liu, C. K. and Blumenfeld, M.: A Study of the Clinical Reactions to Venous Angiocardiography. New England J. Med. **252:** 259 (Feb. 17), 1955.

This report is concerned with 120 patients selected

from a total of 300 cases in which venous angiocardiography was done over a period of eight years at the Stanford Hospital. The ages ranged from 5 days to 68 years. A large variety of cardiac lesions was represented, 77 of the patients being cyanotic and 43, acyanotic. General anesthesia was used in most patients under 12 years of age and local anesthesia was used in those over that age. Only 26 per cent of the patients had no untoward reaction of any kind. In an additional 42 per cent, there were mild reactions, usually consisting of hyperpnea, irregular respiration, cough, tachycardia, bradycardia, nausea and vomiting, urticaria or drowsiness. Severe reactions occurred in 32 per cent of the patients. These included such manifestations as apnea, laryngeal spasm, Cheyne-Stokes respiration, arrhythmias, shock, pulmonary edema, convulsion, syncope and prolonged mental confusion.

There was a single severe reaction (a death) among 24 patients receiving Urokon. This was an incidence of 4 per cent, in contrast to 32 per cent severe reactions to Neo-Iopax and 46 per cent to Diodrast. When Diodrast was used, the incidence of severe reactions increased distinctly when the dose was greater than 1.0 cc. per Kg. of body weight. This feature regarding the size of the dose was not manifest with Urokon or Neo-Iopax. Severe reactions were more frequent in younger patients, in those with cyanosis and when multiple injections were used. Angiocardiography with Neo-Iopax in two patients with obstruction of the superior vena cava was followed by severe thrombophlebitis of the entire external venous system. The slow venous flow in the distended veins and the resulting prolonged contact of the contrast material with the vessel walls were considered important factors in this development.

The authors describe in some detail six fatal cases in their institution out of a total of 300 patients in whom death followed angiocardiography. This represents a mortality of two per cent, a figure comparable to some other reports but higher than that in some series. Cardiac arrest was the cause of death in one child who died immediately after the injection, the other five deaths were classed as late and were due to respiratory failure in four instances and to shock in the fifth. Five of the six patients were in poor general condition. Four of the patients had severe cyanotic congenital cardiac disorders, one had metastatic carcinoma with obstruction of the superior vena cava and one child had idiopathic cardiac hypertrophy with congestive heart failure.

ROSENBAUM

Maluf, N. S. R. and McCoy, C. B.: Translumbar Aortography as a Diagnostic Procedure in Urology with Notes On Caval Phlebography. Am. J. Roentgenol. **73:** 533, (April), 1955.

The authors discuss the technic, complications and diagnostic problems in translumbar aortography and inferior vena caval phlebography, based on their experience in about 250 cases. Among the interesting non-urologic findings were: demonstration of the pharmacologic response to the intra-aortic injection of the dye in a prompt but fleeting fall in blood pressure, followed by a rapid rise to hypertensive levels, returning to normal in about ten minutes and demonstration of aortic, renal arterial, vena caval and renal parenchymal defects. Electric stimulation of the tibial nerve, in the popliteal fossa in an unanesthetized patient with normal kidneys, resulted in appreciable contraction of the renal arteries (previously postulated on experimental evidence by Truetta).

SCHWEDEL

Ragnar, H. and Thalberg, B.: Nomogram for Estimation of the Heart Volume. Acta radiol. **43:** 120 (Feb.), 1955.

A nomogram was constructed to determine the heart volume, using the Jonsell formula which employs the length, breadth and depth of the heart shadow in the numerator, with the square of the body surface in the denominator. A constant (K) is used to correct for the magnification of the heart shadow in the film.

SCHWEDEL

SURGERY AND CARDIOVASCULAR DISEASE

Mazel, M. S., Bernstein, M. M., Callen, I. R., Schnaer, I. L., Wu, L. T. and Bonk, A.: A Simple Operation for the Treatment of Chronic Coronary Artery Disease. Arch. Surg. **70:** 309 (Feb.), 1955.

The authors discuss indications and contraindications for cardiopericardiopexy in the treatment of angina pectoris and present the results obtained in 47 patients. The operation can be performed in about one-half hour. About one and one-half to two drams of U.S.P. talc powder is spread over the heart and blown with an atomizer until the entire myocardium is covered with a thin layer. Then the pericardium is closed loosely. The powder produces a non-constrictive granulomatous pericarditis which hastens the development of inter- and extra-coronary anastomosis.

ABRAMSON

Conference on Therapy: Surgical Treatment of Mitral Valvular Disease. Am. J. Med. **18:** 326 (Feb.), 1955.

Mitral valvulotomy is an accepted surgical procedure with a high incidence of successful results and a mortality reduced to a rate well within that for other operations of similar magnitude. The proper selection of cases is important to reduce surgical mortality and increase the proportion of successful results. In 130 cases at the New York

spital, successful therapeutic results were obtained in 70 per cent. The operative mortality rate was less than 3 per cent. The object of the operation is to increase the size of the mitral orifice. The chief beneficiaries of this operation are patients with mitral stenosis in whom progressive disability from mechanical obstruction at the mitral value is present. The operation is successful in patients with atrial fibrillation or sinus rhythm and often helpful in patients with a mild degree of mitral regurgitation in addition to mitral stenosis. Bacterial endocarditis, active rheumatic fever and severe mitral regurgitation are contraindications to the operation. Cardiac catheterization and clinical manifestations of mitral stenosis are helpful to decide whether operation will be performed. Very light anesthesia, combined with high oxygen intake and administered by a trained anesthetist, is essential for a successful outcome. Psychologic and physical factors must be considered when judging the success or failure of the operation.

HARRIS

Jamison, W. L., Bolton, H. E. and Rao, K. V. S.: Simultaneous Pulmonary Resection for Bronchiectasis and Commissurotomy for Mitral Stenosis. Am. J. Surg. **89:** 279 (Jan.), 1955.

In a series of more than 1000 cases of mitral commissurotomy, the authors found sufficient bronchiectasis to merit surgery in only two. In both of the latter, lobectomy was performed at the same time as mitral commissurotomy. The postoperative course in each instance was stormy, but improvement in the respiratory status was noted subsequently.

ABRAMSON

Barker, N. W.: Surgical Treatment for Arterial Disease. Arch. Surg. **70:** 3 (Jan.), 1955.

The author points out that in the past 30 years the surgical treatment of occlusive, degenerative, traumatic and congenital arterial disease has developed to an extraordinary degree. Autogenous grafts of segments of veins and arteries have been utilized successfully to reestablish the continuity of lacerated or thrombosed arteries. The introduction of heparin, the improvement in anesthesiology and the better means for prevention of postoperative complications have all contributed to the advancements in the field of vascular surgery.

ABRAMSON

Myers, T. T., and Smith, L. R.: Results of the Stripping Operation in the Treatment of Varicose Veins. Proc. Staff Meet., Mayo Clin. **29:** 583 (Nov. 10), 1954.

A postoperative study was made on a large series of patients in whom stripping of varicose veins had been performed, in an attempt to evaluate the procedure. Complications in 1189 procedures consisted of four postoperative episodes of thrombophlebitis and three of pulmonary emboli.

In the cases in which an incomplete stripping was performed, i.e., from the groin to the knee, a 19.3 per cent recurrence was noted two and one-half years after operation. This figure compares with a 2.0 per cent recurrence found when complete radical stripping of all possible varicosities from the dorsum of the foot to the groin was carried out.

The authors concluded that radical stripping is the procedure of choice, since there is less chance of recurrence of skin change and of reoperation. Furthermore, repeated and painful postoperative injections of sclerosing solution are less frequently necessary.

ABRAMSON

Miller, M. I. and Lorhan, P. H.: Clinical Evaluation of Hypotensive Anesthesia. Anesthesiology **16:** 73 (Jan.), 1955.

In 63 patients, high spinal anesthesia was employed to produce a state of hypotension during surgery. The systolic blood pressure was deliberately dropped to 80 mm. Hg or less and was maintained at these levels for periods of one-half to seven and one-half hours, the duration of the surgical procedure in each case. The best results in maintaining this hypotension were obtained with continuous spinal or continuous epidural analgesia rather than with single injections of spinal analgesia. In this series of patients, the induced hypotension apparently aided the operation in that the observed blood loss was minimal and excellent relaxation was obtained during the surgical procedures. In addition, the postoperative course also appeared to be unusually good. The physiologic characteristics of the hypotension produced by spinal anesthesia in these series differed from that observed in the hypotension following arteriotomy in that shock and shock-like signs did not appear.

Because of the sensitivity of hypotensive patients to hypoxia and the inability of these patients to bring about compensatory readjustment of the vascular system following changes in circulating blood volume, it is necessary that blood, oxygen and resuscitative equipment be on hand when this technic is employed. The Trendelenburg position is essential in order to maintain an adequate venous return to the heart and to prevent severe fall in cardiac output. Additional oxygen must be supplied until normal blood pressure levels are established.

The clinical evaluation of this series of 63 cases indicates that in selected patients, where a large blood loss is anticipated during surgery, the hypotensive technic, with its resultant conservation of blood for the patient, offers advantages and benefits for both the patient and surgeon.

SAGALL

Hale, D. E.: Controlled Hypotension. Anesthesiology **16:** 1 (Jan.), 1955.

In a general discussion of the use of controlled

hypotension in surgery, the author points out that this technic may lessen the danger of certain operations by decreasing the amount of blood loss. In addition, controlled hypotension may shorten the duration of operations that might otherwise be prolonged by extensive bleeding which obscures the operative field. Controlled hypotension may be induced by: (1) reduction of the total blood volume by arteriotomy, (2) vasodilatation, produced by spinal anesthesia or (3) by vasodilatation, induced by ganglioplegic drugs such as hexamethonium or Arfonad. The use of controlled hypotension in surgery is contraindicated in the presence of severe coronary disease and in patients who have marked impairment of renal function. The dangers associated with controlled hypotension may be lessened by limiting its use to as short a period as possible and also by insuring adequate oxygenation as well as maintaining a careful control of the blood pressure.

SAGALL

Sadove, M. S., Wyant, G. M., Julian, O. C. and Dye, W. S.: Anesthesia for Mitral Commissurotomy. Anesthesiology **16:** 132 (Jan.), 1955.

The authors present an outline, based upon their analysis of mitral commissurotomy performed on 139 patients, in which they cover the general principles of the management of these patients before, during and after operation.

Preoperative preparation consists primarily of the correction of any existing anemia, electrolyte or water imbalance and improving the nutritional status as well as the cardiac function to its optimal level. Proper selection of the optimal time for operation is essential. Adequate psychologic preparation is necessary and preoperative medication should be kept light, providing sedation without depressing medullary functions.

The special hazards of intracardiac surgery require that certain specialized equipment be instantly available to handle emergency situations. An adequate, efficient transfusion system must be on hand. An electric defibrillator should be connected for immediate use. Various cardiac medications, especially vasopressor drugs, and equipment for continuous oxygen administration should be available.

Anesthesia is induced with Thiopental (Pentothal) sodium and a muscle relaxer, such as dimethyl tubocurarine. After induction of anesthesia, oral endotrachial intubation is performed. The technic employed by the authors utilizes rapid induction and intubation with adequate oxygenation. Anesthesia is maintained with ether and oxygen mixture. The anesthetic plane is deepened during the early phases of the operation, especially as the myocardium is approached. The plane of anesthesia is lightened during the subsequent stages of the operation. After the valvulotomy has been performed and the closure of the pericardium started, the anesthetic agent is changed to a mixture of nitrous oxide and oxygen. In some patients, an intravenous infusion of procaine was administered during the procedure and seemed to result in a diminished need for ether as well as in potentiating the action of the muscle relaxant which was used during induction.

From the results observed in this series, the authors conclude that the method of rapid induction of anesthesia for the operation of mitral commissurotomy is a relatively safe procedure in the presence of adequate precautions.

SAGALL

Hillestad, L.: Surgical Treatment of Arterial Hypertension. Acta med. scandinav. **150:** 41 (Jan. 29), 1955.

This report is based upon observations of 51 cases of essential hypertension, subjected to thoracolumbar sympathectomy over a period of six years and followed-up for periods of 2 to 8 years. The blood pressure was materially reduced in 70 per cent of the cases and 28 per cent had normal blood pressure. Electrocardiographic abnormalities decreased in one-half of the cases and grew worse in 16 per cent of the cases. Of 12 patients with angina pectoris, 7 were improved, 3 unchanged and 2 became worse after operation. Eight other patients developed angina pectoris for the first time after thoracolumbar sympathectomy. Subjective improvement occurred in 70 per cent of the patients. Working capacity was increased in nearly 50 per cent and decreased in one-third of the patients, following operation. Four of the patients died after intervals of 1 to 4 years from the time of operation. A good correlation between the vascular findings in the ocular fundi and the clinical condition was noted by this observer. The conclusion is drawn that operative treatment of hypertension will have a definite place for a long time to come.

ROSENBAUM

Bailey, C. P. and Likoff, W.: The Surgical Treatment of Aortic Insufficiency. Ann. Int. Med. **42:** 388 (Feb.), 1955.

There is a small group of patients in whom highly significant aortic insufficiency, reflected by all the classic clinical findings, has been observed, even though the aortic valve cusps appeared entirely normal at autopsy. The explanation for this apparent paradox rests with the resilience of the annulus fibrosus. When this has been compromised by the pathologic changes incidental to rheumatic activity, the elastic recoil of the aorta at the valve level becomes reduced and coaptation of the cusps, consequently, is imperfect or impossible. If coaptation does momentarily occur, the annulus can not successfully oppose the intra-aortic diastolic pressure which distends the aortic wall in this region, thereby producing valvular incompetence. When

the valve is examined in the living patient through the transaortic approach in such instances, the leaflets are flexible and the commissures are not fixed. In the autopsy room, the ascending aorta will support a column of water. However, clamping of the arch and squeezing of the ascending aorta will result in visible dilatation of the aortic root and leakage into the ventricle. During life, the aortic orifice during systole is normal and the only demonstrable abnormality is a narrow gap between the free margins of the leaflets during diastole which often can be obliterated during transaortic surgery by holding the fingertip in the residual central aperture. This maneuver effectively reduces the regurgitant stream, since the diastolic thrill previously palpable at a point over the left ventricle or the root of the aorta disappears or dramatically diminishes. Withdrawal of the obstructing finger results in a return of the thrill. There is every reason to believe that abnormalities of the cusps and the loss of annular tensile strength may coexist, a situation which is well understood when it occurs in the mitral valve. The development of the transaortic approach for the relief of aortic stenosis has permitted direct digital examination of the valve structures. Applied to the treatment of aortic insufficiency, this method allows digital guidance of the passage and placement of prosthetic materials within the aortic lumen and establishes the degree of narrowing or constricting of the aortic annulus which may be created to insure proper valve function. For the prosthesis, the ball of nylon mesh, suspended by two tails is employed. This material does not cause thrombosis and remains indefinitely strong and flexible in fluid with the pH of blood. This has been placed in the aorta of two individuals with a remarkable change in the level of the diastolic blood pressure. The recommended operation for reducing the size of the aortic annulus is described in detail.

WENDKOS

Leonard, J. J., Harvey, W. P. and Hufnagel, C. A.: Rupture of the Aortic Valve. A Therapeutic Approach. New England J. Med. **252:** 208 (Feb. 10), 1955.

The authors describe a 17 year-old boy who suffered a rupture of the aortic valve when he was kicked in the chest by a horse. This incident was followed by the appearance of severe aortic insufficiency with all the classical peripheral vascular signs and other physical findings. Cardiac catheterization suggested that the patient also suffered a rupture of the interventricular septum. Because the severe aortic insufficiency, induced by rupture of the aortic valve, pointed to probable progressive, rapid deterioration, an artificial aortic valve was inserted in the descending aorta, approximately two months after the accident. Fourteen months after the operation the patient was working full time as a truck driver and the blood pressure in the lower extremities had changed from 180/40 to 115/75 and 125/85. The authors suggest that this same procedure may be applicable when rupture of the aortic valve complicates subacute bacterial endocarditis or occurs in other clinical situations.

ROSENBAUM

De Bakey, M. E., Creech, O., Jr., Cooley, D. A. and Halpert, B.: Failure of Polyethylene Wrapping in Treatment of Aortic Aneurysms. Arch. Surg. **70:** 65 (Jan.), 1955.

The authors had an opportunity to make morphologic studies and clinical observations on eight patients in whom the abdominal aorta, previously treated with polyethylene wrapping, was resected.

Clinically, varying degrees of symptomatic improvement had occurred after the polyethylene wrapping procedure in most of the patients. In a few, this had lasted for about a year. In all, however, there were recurrences of symptoms and progressive increase in size of the aneurysms. Morphologic studies of the resected specimens revealed that the maximal response to the polyethylene consisted of the formation of a thin layer of dense hyalinizing fibrous connective tissue in some areas of the aneurysmal wall, in contact with the polyethylene. In general, the reaction was inadequate to provide significant reinforcement.

It was concluded that the response induced by the implanted polyethylene probably could not have favorably altered the natural course of the aneurysm. At the same time, it might have had an unfavorable effect by its potential tendency to devitalize the sac.

ABRAMSON

Pender, J. W. and Clagett, O. T.: Hypotensive Anesthesia for Radical Mastectomy: Preliminary Report. Proc. Staff Meet., Mayo Clin. 30: 51 (Feb.), 1955.

Data collected during radical mastectomy performed on a group of patients whose blood pressure was decreased by means of hexamethonium are compared with data collected from a group whose blood pressure was kept at preanesthetic levels. The use of induced arterial hypotension, during that part of the operation when the breast was being removed, was advantageous for less hemorrhage occurred and the duration of the operation was decreased. In this small group of patients, no complication occurred which could be attributed to the period of arterial hypotension.

SIMON

THROMBOEMBOLIC PHENOMENON

Towbin, A.: Recurrent Cerebral Embolism. Arch. Neurol. & Psychiat., **73:** 173 (Feb.), 1955.

A cerebral embolism may pursue a subtle, recurrent and chronic course, ultimately leading to

progressive crippling of cerebral function. The onset of symptoms may be insidious and slow and cardiac disease may not be evident. Emboli are often minute and located in "silent areas" of the brain and, therefore, evoke few immediate symptoms. The composite effect of recurrent embolization may lead to progressive cerebral deterioration. Coexistent diseases of the heart and nervous system must be recognized in order to identify the syndrome of cerebral embolism. It may be one of the most important causes of chronic, organic brain disease.

Clinically, the diagnosis is extremely difficult. It is based on a history of protracted heart disease, neurologic symptoms appearing in the fourth or fifth decade and sharp episodes of new and recurrent neurologic symptoms which gradually lead to central nervous system deterioration. At autopsy, typically, there is chronic cardiac disease with mural thrombi in the left side of the heart and focal infarcts of varying ages in the brain with arterial occlusion in the region of infarction, with little cerebral arteriosclerosis. Autopsy offers the only valid basis for estimating the incidence of this clinically deceptive process.

In a state mental institution, the brains of 525 autopsies were examined, and the results correlated with the clinical data. Seventeen cases of recurrent cerebral embolism were found. The case histories and autopsies are recorded. Clinically, the diagnosis was made only once. Of the 17 cases, 11 were associated with myocardial infarction, five with old rheumatic heart disease and one with non-bacterial thrombotic endocarditis. The results indicated that this is a disease of young adulthood and middle age, that the neuropsychiatric symptoms may persist for from several weeks to 30 years and that the cerebral pathology may vary. Of 54 cases of coronary occlusion, 14 had normal thrombi and 10 of these had recurrent embolization of the brain. Of 34 cases of old rheumatic heart disease, five showed evidence of recurrent embolization of the brain. The embolization may occur many years after the cardiac damage.

Cerebral embolism occurs more often than is generally realized. Recent advances in the treatment of thromboembolic disease make this diagnosis very important.

WECHSLER

VASCULAR DISEASES

Elliott, A.: Hypercholoremia, Azotemia and Pulmonary Edema of Cerebral Origin. Acta med. scandinav. **150:** 467–476, (Jan. 29) 1955.

A woman, 54 years old, is described in detail. Two and one-half months after an episode of retrobulbar neuritis there was a sudden onset of apathy, pulmonary edema, hyperchloremia, hypochloruria, azotemia, leucocytosis and neurologic manifestations including left-sided hemihypesthesia, left-sided signe de rideau, partial hemiopsia, postural nystagmus and loss of abdominal reflexes. There was almost complete regression of the abnormalities in a few weeks. The author expresses the opinion that multiple sclerosis is the probable diagnosis. The cerebral lesions responsible for the clinical syndrome are reviewed in detail. It is mentioned that a single lesion of the supraoptic nucleus on the left side of the lower hypothalamus could theoretically be responsible. However, the author is inclined to believe that the failure in the function of the pulmonary circulation resulted from an imbalance of several different centers, either as a result of irritation of one center or unsatisfactory functioning of some other center.

ROSENBAUM

Keates, P. G. and Magidson, O.: Dysphagia Associated with Sclerosis of the Aorta. Brit. J. Radiol **28:** 184 (April), 1955.

The authors have collected seven cases in which dysphagia was associated with pressure in the esophagus from a sclerotic and unfolded aorta. All of the cases were elderly women, four with hypertensive heart failure and another with arteriosclerotic heart disease with failure. In three cases other causes of dysphagia were excluded by esophagoscopy. Indentations, seemingly compressive, may be found in the mid thoracic or lower thoracic portions of the aorta, possibly due to the location of the esophagus between the tortuous aorta and the enlarged left ventricle. At times change from the upright to the recumbent position may bring out the characteristic defects. The authors indicate that in other patients the same radiographic picture may not be associated with dysphagia.

SCHWEDEL

Berlin, L., Tumarkin, B. and Marlen, H. L.: Cerebral Thrombosis in Young Adults. New England J. Med. **252:** 162 (Feb. 3), 1955.

A group of 13 patients ranging in age from 18 to 37 years is described. These patients were all observed within a period of three years. Each patient had a sudden onset of focal neurologic signs without evidence of other neurologic or systemic disease. The initial manifestations included hemiplegia, mental clouding, somnolence, aphasia, diplopia or convulsive seizures. Gradual improvement but often with residual hemiparesis followed in all but a single fatal case. The blood pressures, pulse rates and cardiac rhythms were normal in all cases. Serologic tests of the blood and spinal fluid for syphilis were negative in all patients. Diabetes mellitus was excluded in all instances. The authors attribute the thrombosis in these cases to occlusive vascular disease such as arteriosclerosis. The illness developed in a setting of a stressful life situation in several instances and the authors mention the fact that it is possible that such situations may alter

bodclotting mechanisms and blood viscosity or crease resistance to blood flow, thereby contributg to the development of the cerebrovascular sions.

ROSENBAUM

insell, L. W., Michaels, G. D. and Foreman, N.: High Vegetable Diet in Diabetics with Extensive Vascular Disease. Geriatrics **10:** 67 (Feb.), 1955.

A diet consisting of fat, all of vegetable origin, was d to elderly diabetics with peripheral vascular isease and to juvenile diabetics with evidence of idespread vascular disease, including retinopathy nd nephropathy. The former group was observed n an ambulatory basis, the latter under precisely ontrolled conditions on a metabolic ward. In he first group, serum lipids could be brought to normal on this diet but no comment could be made on the effect on clinical benefit. On the second group, the diet seemed to improve the retinal status but had no effect on the renal status.

RINZLER

de Takats, G.: Revascularization of the Arteriosclerotic Extremity. Arch. Surg. **70:** 5 (Jan.), 1955.

The various means for vascularization of an ischemic extremity are discussed and evaluated by the author. These consist of removal of clots, reaming out an atheromatous vessel, excision of the occluded segment and re-establishment of the continuity of the lumen, using a venous or arterial graft and sympathectomy. The problem of whether a successful result can be expected is intimately tied with methods of prevention and methods of arresting the rate of progress of arteriosclerosis.

ABRAMSON

Clarke, N. E., Clarke, C. N., and Mosher, R. E.: The "*in vivo*" Dissolution of Metastatic Calcium. An Approach to Atherosclerosis. Am. J. M. Sc. **229:** 142 (Feb.), 1955.

The disodium salt of ethylene diaminetetraacetic cid (EDTA) was administered intravenously as a olution of 5 Gm. of the salt in 500 cc. of 5 per cent lucose or saline. Patients with nephrocalcinosis, oronary artery disease, calcific mitral stenosis and ther diseases associated with calcium deposition in issues were treated in this fashion. An average umber of 50 injections was given per patient. The oxic manifestations of this treatment included a urning sensation at the site of the infusion, nausea nd diarrhea and abdominal cramps in several atients; dermatitis and mucous membrane lesions eveloped in 9 patients. The administration of yridoxine was noted to reduce the incidence and everity of the toxic reactions. Normal serum calcium levels were maintained during the treatment period. Roentgenograms are shown which demonstrate removal of significant amounts of calcium from the renal parenchyma of a patient with nephrocalcinosis. Otosclerosis was favorably affected with a striking improvement in hearing being noted after EDTA treatment. No statement is made concerning its effect upon angina pectoris or the other diseases treated.

SHUMAN

Nylin, G. and Blömer, H.: Studies Concerning Cerebral Circulation using Radioactive Isotopes (Preliminary Report). Ztschr. Kreislaufforsch. **44:** 139, (Feb.), 1955.

In 14 experiments on 12 patients, the authors attempted to determine quantitatively cerebral blood flow using erthrocytes labelled by radioactive thorium (thorium B). The theoretic basis and the method used are described in detail. Data obtained in three patients, referring to magnitude of cerebral flow and oxygen consumption of the brain, correlated well with values reported in the literature. The possibility of application of the method to the localization of brain lesions to the right or left hemisphere is discussed.

PICK

Patterson, J. W.: Effect of Blood Supply on the Development of Cataracts. Am. J. Physiol. **180:** 495 (March), 1955.

The initial cataract from feeding galactose in rats may appear in either eye, although a few more appear on the left. If one carotid artery is ligated and galactose is fed, the cataract appears on the unligated side. This is the side with the better blood supply and, hence, exposure to galactose. In diabetic rats, the first cataract appears on the left in 52 per cent but this is unaffected by carotid ligation on one side. The author suggests that on this basis high glucose levels are not directly responsible for the cataract. It is further suggested that lack of insulin may be concerned.

OPPENHEIMER

Altschul, R.: The Effect of Oxygen Therapy upon Experimental Cholesterol Atherosclerosis. Ztschr. Kreislaufforsch. **44:** 129, (Feb.), 1955.

Eighteen rabbits were fed 0.3 Gm. cholesterol daily for three months and during this time submitted three times a week to breathing of 60 to 65 per cent oxygen. In 15 animals it was possible, partially or totally, to prevent the development of atheromatous lesions in the aorta and organ arteries. This is ascribed by the authors to increased oxidation of cholesterol in the blood and in the tissues.

PICK

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

1956 HEART FUND

The eighth annual Heart Fund campaign of the Association will be conducted throughout the month of February. The atmosphere of greatly heightened public interest in the subject of cardiovascular problems strengthens the belief that contributions to the Heart Fund will once again show a substantial increase over those of all previous years. The 1955 Heart Fund totaled $13,575,963, as compared with $11,330,195 in 1954.

If the expectations of increased public support are realized, it will mean more money than ever before to finance the Association's programs of scientific research, professional and lay education and community service. Greatest emphasis, of course, is placed on research support. At least half of all monies received by the National Office are allocated to research. In addition a substantial portion of the funds retained by the affiliated Heart Associations are utilized in support of scientific investigation. Since 1948, when the Association became a national voluntary health agency, more than $13,000,000 have been expended in support of research by national, state and local Heart Associations.

For the third consecutive year, General Mark W. Clark, now President of the Military College of South Carolina (The Citadel) in Charleston, will serve as National Campaign Chairman of the Heart Fund. He will be aided by Co-Chairman Edward V. Rickenbacker, Chairman of the Board of Eastern Airlines.

February 26 has been designated as Heart Sunday. On that date, communities from coast to coast will hold concentrated house-to-house collections.

As in the past, the medical profession will play a key role in the Heart Fund drive. Because the campaign is designed to raise the level of public understanding of cardiovascular diseases as well as to raise funds, many Heart Associations are enlisting physicians as speakers and committee members. In this way, the latest advances in cardiovascular research and treatment will be accurately reported to the public.

HIGH BLOOD PRESSURE COUNCIL NAMES MEDICAL AND LAY LEADERS

Thomas Findley, M.D., Professor of Medicine at the Medical College of Georgia, Augusta, was elected Chairman of the Medical Advisory Board of the Council for High Blood Pressure Research at its annual meeting in Cleveland, November 18 and 19. Dr. Findley, formerly vice chairman, was named to succeed Eugene B. Ferris, M.D., Professor of Medicine at Emory University, Atlanta.

The new vice chairman of the board is Meyer Friedman, M.D., Associate Chief of the Department of Medicine, Mt. Zion Hospital, San Francisco.

The Council re-elected Maynard Hale Murch, Cleveland, as its President. Mr. Murch, who will be serving his second term, is president of the investment banking firm which bears his name.

ATHEROSCLEROSIS SYMPOSIUM PROCEEDINGS PUBLISHED

The proceedings of the Symposium on Atherosclerosis conducted in 1954 by the National Academy of Sciences – National Research Council at the request of the U. S. Air Forces are now available.

Purpose of the publication was to gather in one volume current information bearing on the development of diagnostic and predictive criteria and at the same time to bring into clearer focus the present status of research and the most promising avenues for future investigation. It is particularly recommended for those engaged or interested in arteriosclerosis research and is oriented toward a continuing research effort.

The proceedings constitute a review of fun-

dimental knowledge concerning the etiology and pathogenesis of atherosclerosis. In addition to the texts of 23 papers presented at the symposium, the volume contains an introduction by Irvine H. Page, M.D., President of the American Heart Association, who chaired the symposium. The papers present and analyze pertinent information on the anatomy and physiology of the blood vessel wall, its responses to injury and other influences, the role of nutrition, and the metabolism of lipids and lipoproteins. A section is devoted to the application of new techniques such as polarization optics, x-ray diffraction and absorption and electron microscopy.

The 249-page volume is priced at $2.00 Orders should be sent to the National Academy of Sciences – National Research Council, Publications Office, 2101 Constitution Avenue, Washington 25, D. C.

MAY 15 ABSTRACTS DEADLINE SET FOR 1956 SCIENTIFIC SESSIONS

May 15 has been set as the deadline for submission of abstracts by those interested in presenting papers to the 1956 Scientific Sessions of the American Heart Association. These sessions will be conducted October 27–29 in conjunction with the Association's Annual Meeting in Cincinnati (October 27–31).

Papers intended for presentation should be based on original investigations in or related to the cardiovascular field. The abstracts should contain in summary form the results obtained and the conclusions reached. All abstracts accepted for either presentation or publication will be published in the "Proceedings" without change, so they should be submitted in final form.

In order to be considered, abstracts must be submitted on forms available from the Association. They should not exceed 300 words in length, and they must be submitted in triplicate. The full names of all authors must be included, as must the name of the person who plans to make the actual presentation. More complete instructions will be sent to those requesting the necessary forms from the Medical Director, American Heart Association, 44 East 23 Street, New York 10, N. Y.

HEALTH COUNCIL PLANS FORUM ON CHRONIC ILLNESS

A two-day forum on problems of chronic illness will be conducted March 21 and 22 in New York by the National Health Council as a part of the annual National Health Week observation. The forum will be under the chairmanship of Theodore G. Klumpp, M.D., president of Winthrop-Stearns, Inc.

In designating the subject for the forum, the Board of the National Health Council indicated that it hoped the discussions would help to "identify specific activities under way to improve the care of the long-term patient" and "point up community responsibility for concerted action on chronic illness."

The National Health Week program will run March 18–24. It will be sponsored by the United States Junior Chamber of Commerce in cooperation with the National Health Council. The Junior Chamber is distributing materials for local programs to its chapters throughout the country.

National Health Council members include a number of voluntary health agencies including the American Heart Association.

KANSAS OFFERS GRADUATE TRAINING PROGRAMS

In-residence training in the fields of cardiovascular and pulmonary diseases is being offered by the University of Kansas Medical School Department of Medicine.

The postgraduate opportunities are available to two physicians in each of the fields for one month. Courses are as follows: Cardiovascular Disease–March 1, April 1, May 1; Pulmonary Disease–April 1, May 1.

Participants in the program will have opportunities to obtain supervised experience in many newer techniques and in patient care and management of cardiac and pulmonary diseases. Applications should be directed to the Department of Postgraduate Medicine Education, Kansas University School of Medicine, Kansas City, Kan.

MINNESOTA OFFERS COURSE FOR INTERNISTS

A course in Recent Advances in Internal Medicine for internists will be conducted at the

University of Minnesota's Center for Continuation Study in Minneapolis, February 13–15. This year's program will deal with recent advances in knowledge of endocrinology and metabolism, renal disease and cardiology.

Guest speaker will be Joseph W. Jailer, M.D., Associate Professor of Medicine at the College of Physicians and Surgeons of Columbia University, New York. The course will be under the direction of C. J. Watson, M.D., Professor of Medicine at Minnesota. Information may be obtained from Robert B. Howard, M.D., Director, Department of Continuation Medical Education, University of Minnesota Medical School, Minneapolis 14, Minn.

SEATTLE HOSPITAL SEEKS PEDIATRIC CARDIOLOGY FELLOWS

Availability of one or two fellowships in pediatric cardiology beginning July 1956 has been announced by the Children's Orthopedic Hospital in Seattle. Training will be conducted in conjunction with the Department of Pediatric Cardiology of the University of Washington Medical School.

Applicants should have a minimum of two years of pediatrics. Full information may be obtained from Robert A. Tidewell, M.D., The Children's Orthopedic Hospital, 4800 Sand Point Way, Seattle 5, Wash.

MEETINGS CALENDAR

Jan. 20: Southern Section, American Federation for Clinical Research, New Orleans. John H. Moyer, M.D., Baylor University College of Medicine, 1200 M. D. Anderson Blvd., Houston.

Jan. 25: Western Section, American Federation for Clinical Research, Carmel, Calif. B. H. Scribner, M.D., Veterans Administration Hospital, Seattle 8, Wash.

Feb. 6–8: American Academy of Allergy, St. Louis, Francis C. Lowell, 65 E. Newton St., Boston.

Feb. 10–11: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Drive, Chicago 6.

March 24–25: American Psychosomatic Society, Sheraton Plaza Hotel, Boston. Stanley Cobb, M.D., 551 Madison Avenue, New York 22.

April 4–6: American Association of Anatomists, Milwaukee. Normand L. Hoerr, 2109 Adelbert Rd., Cleveland 6.

April 15–20: American Society for Pharmacology and Experimental Therapeutics, Atlantic City. C. C. Pfeiffer, Emory University School of Medicine, Emory University, Ga.

April 15–20: American College of Allergists, New York. F. W. Wittich, 401 Marquette Bank Bldg., Minneapolis 2.

April 15–21: American Society for Experimental Pathology, Atlantic City. Cyrus C. Erickson, 87 Union Ave., Memphis 3.

April 26–28: American Association of Pathologists and Bacteriologists, Cincinnati. Edward A. Gall, Cincinnati General Hospital, Cincinnati 29.

April 27–28: American Gastroenterological Association, Atlantic City, H. Marvin Pollard, University Hospital, Ann Arbor, Mich.

April 29: American Federation for Clinical Research, Atlantic City. William W. Stead, V.A. Hospital, Minneapolis 17.

April 30: American Society for Clinical Investigation, Atlantic City. A. O. DeWeese. 515 East Main Street, Kent, O.

ABROAD

Jan. 20–27: Pan-American Congress of Gastro-Enterology, Havana. Dr. Norberto E. Stapler, 1667 J. E. Uriburu, Buenos Aires.

Jan. 22: French Assembly of General Medicine, 53rd Medical Meeting, Paris. Dr. Guy Godlewski, 157 Avenue Malakoff, Paris 16e.

March 6–9: Ciba Foundation Symposium on Influence of Ionizing Radiation on Cell Metabolism (by invitation), London. Dr. G. E. W. Wolstenholme, Director of Foundation, 41 Portland Place, London W.1.

March 26–28: Ciba Foundation Symposium on The Biophysics and Biochemistry of Viruses (by invitation), London. Dr. G. E. W. Wolstenholme, Director of Foundation, 41 Portland Place, London, W.1.

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Continued from page 159

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NOTICE TO CONTRIBUTORS

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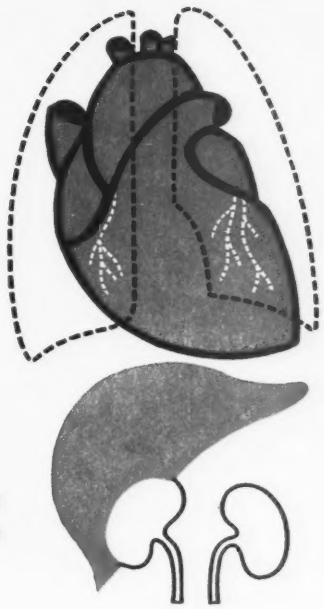
know your diuretic



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